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Volume 83 Number 9 September 1996

CUK-H06234-36-P25349

The British Journal of SURGERY

CODEN BJSUAM ISSN 0007-1323

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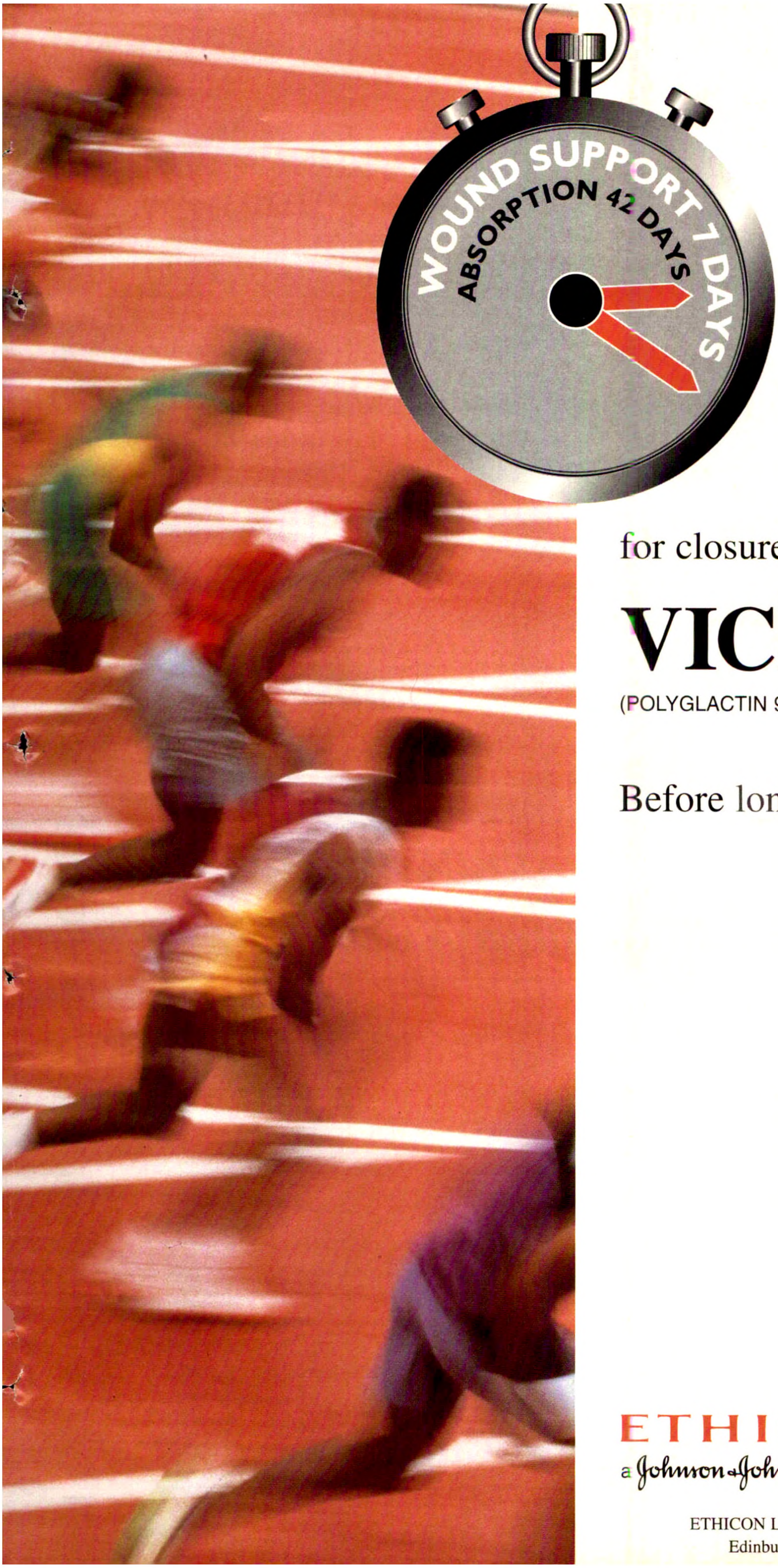

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THE AUSTRALIAN AND NEW ZEALAND JOURNAL OF SURGERY

Chairman &
Editor in Chief
G. J. A. Clunie

ISSN 0004-8682
Published monthly

Editors
J. Ludbrook
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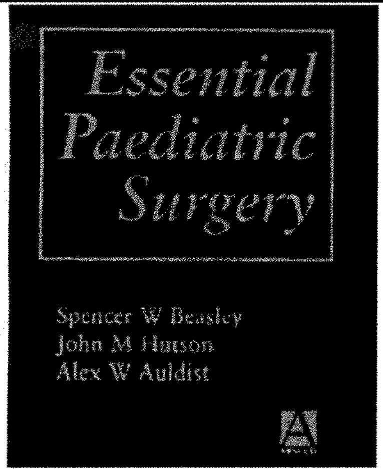

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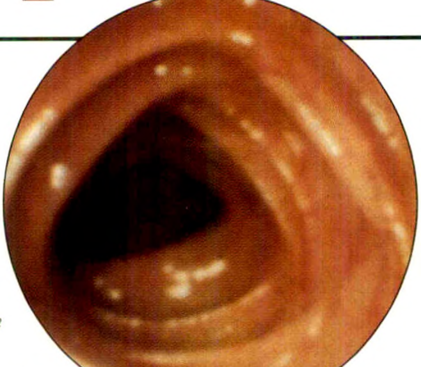

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British Journal of Surgery 1996, 83, 1169–1170

Leading articles

Laparoscopic appendicectomy

Laparoscopic appendicectomy was first described in the early 1980s but has never become popular. A recent audit on behalf of the Royal College of Surgeons of England suggested that only 1·2 per cent of patients undergoing appendicectomy had a laparoscopic operation[1]. Is laparoscopic appendicectomy dying from natural causes or neglect?

There are two possible advantages of the laparoscopic procedure over conventional open surgery: first, the diagnostic value of laparoscopy itself and, second, improved postoperative recovery. If one is convinced of the value of diagnostic laparoscopy, going on to remove an inflamed appendix thus found by a laparoscopic technique requires minimal additional effort. If one is not convinced, laparoscopic surgery must prove to offer significant advantages in its own right if it is to be attractive.

Diagnostic laparoscopy for suspected appendicitis is more accurate than clinical diagnosis. Potentially, two approaches might be adopted: to carry out laparoscopy on all patients admitted to hospital with acute abdominal pain, or to perform laparoscopy only when the clinical diagnosis of appendicitis has been made and the decision taken to operate. The former policy effectively replaces expectant management of lower abdominal pain. It allows earlier treatment of patients in whom the clinical diagnosis of appendicitis is not certain, but a high proportion of patients then subjected to laparoscopy will have a normal appendix and many of these could be managed expectantly. Diagnostic laparoscopy may 'save' many patients from having a normal appendix removed, but only at the cost of an invasive diagnostic test with its own morbidity[2]; this outweighs the benefit of earlier diagnosis. Other options, such as computer-aided diagnosis, ultrasonography or barium enema, may achieve improved diagnostic results more cheaply and with less morbidity[3]; the problem with these in most hospitals in the UK is lack of availability within a short timespan.

When a diagnosis of appendicitis is reached on clinical grounds and a decision made to operate, typically 20–30 per cent of patients are found to have a normal appendix. In adults, diagnostic laparoscopy reveals an alternative pathology in approximately half of these patients (10–15 per cent of the total); the remainder have no obvious pathology. Most, but certainly not all, of the patients with other pathology will be female. At open operation, however, it is also possible to detect pathology other than appendicitis, although the proportion is less than at laparoscopy. Thus, diagnostic laparoscopy has the ability to establish a diagnosis that would otherwise have been missed in up to one in 20 patients with suspected appendicitis. In many of these the management will be altered as a result. As over 40000 appendicectomies are carried out annually in England and Wales this may be important but, for an individual surgeon treating about 40 patients a year, the value of laparoscopy may appear unimpressive or non-existent.

Data assessing recovery after laparoscopic appendicectomy are available from several prospective randomized trials comparing open and laparoscopic surgery[4–8]. There is little difference between the operations in terms of postoperative pain. A shorter hospital stay after laparoscopic surgery is reported by some but not by all; this important outcome measure is difficult to assess as observer bias is possible, length of stay varies from one study to the next, and very short stays have been achieved after open surgery on which it would be hard to improve. Once at home, recovery may be faster after laparoscopic surgery and return to work earlier but, in truth, the differences are small and none of the studies is large enough to be convincing. A meta-analysis that is being undertaken by the University of Otago may provide a definitive answer.

A major difference between open and laparoscopic surgery is noted in wound complication rates, which are significantly reduced from up to 20 per cent after open surgery[9] to less than 5 per cent after laparoscopic surgery. All the available comparative studies[4–8] employed up-to-date antibiotic prophylaxis in all patients, and all reported fewer wound infections after laparoscopic surgery with a statistically significant difference in most reports. In addition, the wounds of laparoscopic appendicectomy are generally cosmetically better. Most surgeons claim they can remove an appendix through a very small incision but, with the exception of a small minority of the population, a given patient will have a smaller scar after laparoscopic than after open surgery, and the fatter the patient, the greater the difference. Smaller scars may not be the most important consideration but, all else being equal, they are preferred by the patient and may allow a faster recovery.

Laparoscopic appendicectomy probably costs more than the open operation, although some cost may be saved from reduced wound infection. Operating time is generally slightly longer than for open surgery, but this difference is of little practical or clinical significance, and the time improves with experience. Rates of conversion to open operation, typically between 10 and 20 per cent, are very low in some of the largest series, and there is no doubt that laparoscopic appendicectomy can be a demanding operation. Nevertheless, in no randomized study was the morbidity rate significantly greater than that of open surgery. It is also worthy of consideration that laparoscopic appendicectomy is an excellent procedure for training young surgeons and it may be a safer introduction to laparoscopic skills than laparoscopic cholecystectomy.

Appendicectomy is usually undertaken by trainees who do not have the experience or confidence in laparoscopy to use it routinely. It is an operation that is frequently done 'out of hours' when there are limited staff available who are, perhaps, unfamiliar with laparoscopic equipment; training may have to take second place to 'getting the job done'. The perception of surgeons who actually do the majority of appendicectomies appears to be that laparoscopic surgery is not worth the trouble and that they do not have sufficient experience of the technique. The diagnostic benefits of laparoscopy are small, as are the benefits of removing an inflamed appendix by laparoscopic means. Perhaps the combination of such benefits requires more careful consideration than it has so far been given, but the price of achieving this would be greater input from experienced surgeons into the teaching of the operation.

J. J. T. Tate

Department of Surgery
Royal United Hospital
Bath BA1 3NG
UK

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British Journal of Surgery 1996, 83, 1171–1173

Percutaneous transluminal angioplasty of the internal carotid artery

The place of endarterectomy in both symptomatic and asymptomatic patients with varying degrees of internal carotid artery stenosis has now been established by several large clinical trials. No such trials evaluating the risks and benefits of percutaneous transluminal balloon angioplasty of the carotid vessel have yet been undertaken, although the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), largely based at St George's Hospital in London and the Royal Northern Infirmary in Sheffield, is well underway.

Balloon angioplasty of the internal carotid artery was first performed in a patient with fibromuscular dysplasia and the technique was rapidly adopted for this condition[1]. The indications for carotid balloon angioplasty have now been extended to include atherosclerotic, vasculitic and radiation-induced stenosis. The procedure has, more recently, been used to dilate recurrent stenosis of the carotid vessels occurring after surgical endarterectomy or previous percutaneous transluminal angioplasty. These developments have been met with both enthusiasm and anxiety.

The potential benefits of percutaneous transluminal angioplasty of the carotid artery are avoidance of general anaesthesia, a short procedure time, a short hospital stay compared with that associated with carotid endarterectomy and, hopefully, a reduction in morbidity and mortality. However, almost all patients can be discharged 48 h after carotid endarterectomy and in one study the catheter technique required an average of 1·7 (range 1·5–2) h to perform[2].

The main concern about balloon angioplasty has been the risk of cerebral embolization, which is a recognized complication of carotid angiography. Monitoring by transcranial Doppler ultrasonography has demonstrated particulate embolization during carotid endarterectomy, carotid angiography and carotid balloon angioplasty. In one small study, embolization after percutaneous transluminal angioplasty was found to be common but usually symptomless[3]. Some authors have advocated that the catheter technique be combined with surgical exposure of the carotid artery in order to reduce the risks of blind arterial catheterization, while others have advocated the use of a balloon blocking system inserted into the distal internal carotid artery to trap any embolic material dislodged by the dilatation[4,5].

Problems of cerebral ischaemia may be anticipated in patients with a discontinuous circle of Willis because the carotid blood flow is completely obstructed during balloon inflation. A preliminary balloon occlusion test has been used to determine the effects of flow interruption. In one study this test alone caused three of 14 patients to develop a transient hemiparesis or sensory disturbance[2]. A shunt can always be inserted during surgical endarterectomy when there is evidence of cerebral ischaemia or poor middle cerebral blood flow; this option is obviously not possible during the percutaneous catheter procedure.

Reported complications of balloon angioplasty include failure to manipulate the guide-wire past the stenosis (in one series in 32 per cent of cases)[6] and arterial dissection following incorrect placement of the wire. Transient ischaemic attacks, transient strokes, completed strokes, haematoma formation, thrombosis, late ischaemic events and restenosis have all now been documented. One study[7] found that 51 per cent of awake patients experience cervical pain during the procedure. Another[2] reported transient bradycardia and hypotension during or after angioplasty in nine of 16 patients. In view of the anatomically widespread nature of atherosclerosis, it is surprising that there have not yet been any reports of false aneurysm or embolic complications affecting the distal limb after femoral or brachial catheter insertion; these are well recognized complications of coronary angiography and balloon angioplasty. There are also no reports to date of haemorrhage from the percutaneous insertion site.

Some authors have suggested that the results of balloon angioplasty for recurrent internal carotid artery stenosis following endarterectomy are disappointing. In one report[8], three patients had an attempted balloon angioplasty of surgical restenosis in the proximal internal carotid artery. One patient developed reversible spasm and transient stroke, while dissections developed in the other two. One of these dissections was further complicated by embolism and stroke, while the other was complicated by a transient ischaemic event that required operative thrombectomy and surgical bypass[8]. At present, it is impossible to arrive at any firm conclusion on the place of balloon angioplasty for recurrent carotid stenosis as most reports describe small numbers of patients followed for short periods. The potential use of stents adds yet another dimension. Their use in some circumstances may be advantageous but the late effects, including myointimal hyperplasia, need to be assessed. One study reported that two of six patients who had balloon angioplasty after surgical endarterectomy required reangioplasty at 6 months; a Palmaz stent (Johnson and Johnson, Bracknell, UK) was deemed necessary in one patient[8].

Several questions remain unanswered. Is the catheter technique safer to perform through a closed percutaneous femoral, brachial or carotid route, or using an open approach with distal carotid clamping? Should a percutaneously inserted balloon positioned in the distal internal carotid artery be inflated before dilatation of the narrowed segment? Is endarterectomy after a balloon angioplasty failure or restenosis more or less hazardous than endarterectomy after operative restenosis? Are some carotid plaques more dangerous to negotiate than others? Do certain characteristics of plaques render them less suitable for balloon dilatation?

Finally, little is known about long-term patency after balloon angioplasty of the carotid artery. Mean follow-up periods vary; a mean of 67 months was reported in one study[9]. Reported ranges also vary, from as little as 1 month to up to 7 years[10]. Yamamura *et al.*[2] have described significant restenosis in three of 16 patients followed for an average of 15·7 months. Markus *et al.*[3] reported significant restenosis in two of ten patients by 1 month.

Despite its potential advantages, percutaneous transluminal balloon angioplasty of the internal carotid artery remains an experimental procedure. Until the results of the CAVATAS become available, such treatment outside trial centres should probably be reserved for patients with particular indications, including surgically inaccessible lesions, significant concomitant medical conditions and fibromuscular dysplasia. The results should be audited carefully.

C. L. McGuinness
K. G. Burnand

Department of Vascular Surgery
St Thomas' Hospital
Lambeth Palace Road
London SE1 7EH
UK

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Editors' announcement

Illustrations in colour

The Journal does not contain many illustrations in colour at present, probably because authors are usually requested to make a contribution towards the cost of colour reproduction. This cost is substantial, amounting to approximately £500 per figure at current rates. In association with the publishers, Blackwell Science Ltd, The British Journal of Surgery Society is keen to increase the number of colour illustrations in the Journal. The use of colour is particularly appropriate for operative photographs (whether open operation or laparoscopy), resection specimens and especially photomicrographs. To encourage the submission of suitable illustrations in colour, authors' charges will be waived. Three high-quality prints of each figure should be submitted.

R. C. N. Williamson
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J. J. Earnshaw
P. J. Guillou

British Journal of Surgery 1996, 83, 1174–1185

Review

Risk factors for squamous cell carcinoma of the oesophagus

U. RIBEIRO JR, M. C. POSNER, A. V. SAFATLE-RIBEIRO* and J. C. REYNOLDS*

*Departments of Surgery and *Gastroenterology, University of Pittsburg Medical Center, Pittsburgh, Pennsylvania, USA*
Correspondence to Dr J C Reynolds, Division of Gastroenterology and Hepatology, University of Pittsburgh Medical Center, Presbyterian University Hospital, 200 Lothrop Street, M Level, C Wing, Pittsburgh, Pennsylvania 15 213, USA

Cancer of the oesophagus has great diversity in geographical distribution and incidence. The rate of oesophageal cancer has been increasing in some areas and the reasons for this are not clear. This review outlines fascinating epidemiological aspects and the risk factors for squamous cell carcinoma of the oesophagus. While in the Western world the effects of alcohol and tobacco are substantial preconditions, worldwide other factors, such as diet, nutritional deficiencies, environmental exposure and infectious agents (especially papillomavirus and fungi), play a significant role. Chronic irritation of the oesophagus appears to participate in the process of carcinogenesis, particularly in patients with thermal and/or mechanical injury, achalasia, oesophageal diverticulum, chronic lye stricture, radiation therapy, injection sclerotherapy and gastric resection before the appearance of oesophageal tumour. The association of Plummer–Vinson syndrome, coeliac disease, tylosis and scleroderma with oesophageal cancer has also been reviewed.

Oesophageal cancer is the sixth most common cancer in the world and one of the most lethal tumours[1]. Squamous cell carcinoma (SCC) is the predominant histological type of oesophageal cancer worldwide, although in the USA and Europe the incidence of adenocarcinoma of the oesophagus and gastric cardia, including the oesophagogastric junction, has been increasing rapidly, especially among white men[2,3]. Advances have occurred in surgical technique, chemotherapy, radiation therapy and palliative measures, such as photodynamic therapy, laser therapy, and endoscopic stenting. Despite these innovations, there has been no discernible improvement in the prognosis of this disease which is associated with a 5-year survival rate of approximately 5 per cent. While no single cause of SCC has been identified, several factors are postulated to play a role in the development of SCC of the oesophagus and their effects may be additive or even synergistic. For several factors, there is a clear dose–response effect that persists even after adjustment for other possible risk factors. This review does not discuss adenocarcinoma and its association with Barrett's metaplasia, but instead focuses on risk factors for SCC.

Epidemiology

The wide geographic and cultural variation in incidence of SCC of the oesophagus suggests that environmental exposure is causally important[4,5] (*Table 1*). Regions with a high incidence of the disease are generally located in poor parts of the world whose inhabitants share several dietary characteristics[4,6]. They subsist on a diet high in starch and low in fresh fruit and vegetables, eat rapidly without sufficient mastication, and consume many foods and drinks at very high temperatures[6]. In the Western world, the incidence of SCC of the oesophagus varies among racial and socioeconomic groups[4,7–9]. Generally, lower socioeconomic groups have a higher risk[4,7–9]. In the USA blacks have a relative risk that is fourfold higher than that of whites[4,8]. Additionally, the incidence of cancer of the oesophagus is inversely related to level of education achieved[10].

Some geographic areas have an extremely high incidence, up to one per 1000 adults[4,11] A so-called 'Asian oesophageal cancer belt' stretches from eastern Turkey and east of the Caspian Sea through northern Iran, northern Afghanistan and southern areas of the former Soviet Union, such as Turkmenistan, Uzbekistan and Tajikistan, to northern China and India[4,5,11]. SCC of the oesophagus is also common among distinct populations in certain parts of Africa (the Transkei region of Cape Province and Kenya)[4,5,12] and among people with a regular intake of tea-rice gruel in a high-risk area of Japan[13]. Worldwide, men are more frequently affected than women, although the sex distribution shows considerable regional variation[4,11,14,15]. The causes of the higher male risk is unclear, but probably reflects sex-related

Table 1 Incidence of oesophageal cancer in different regions of the world

		Incidence per 100 000	
Region	Locality	Men	Women
Asian oesophageal cancer belt		> 100	> 100
China	Yangcheng	135·2	84·4
	Tianjin	16·6	8
India	Kashmir	42·6	27·9
	Bombay	11·4	8·9
	Bangalore	6·6	5·3
Europe			
Northern Europe		< 4·0	< 2·0
Eastern Europe		< 4·0	< 2·0
France	Calvados	26·5	—
UK	East Scotland	8.5	4·3
	England and Wales	6·5	3·2
South America			
Uruguay		40	—
Brazil	Porto Alegre	26·3	7·8
North America			
USA	Los Angeles	16·4	4·9
	Washington DC Black	16·9	4·5
	White	4·1	1·7
Africa			
Transkei		37·2	21·1

Paper accepted 29 February 1996

differences in diet, smoking and/or alcohol consumption. In the Asian oesophageal cancer belt, where environmental factors are thought to be aetiological, men and women are affected with equal frequency[4,5,6,15].

Histological precursors of squamous cell carcinoma of the oesophagus

Several lesions have been described in the malignant transformation of the oesophageal epithelium, including chronic oesophagitis, papilloma, atrophy, dysplasia and carcinoma *in situ*. The high prevalence of these lesions, even in the younger members of high-risk groups, the multifocality and the presence of concurrent cancer affecting the same sections of the oesophagus suggest that these lesions are associated[16,17]. Moreover, findings from follow-up studies have shown progression of chronic oesophagitis to more advanced lesions (atrophy, dysplasia and cancer) in the same regions that harbour oesophagitis[18]. Several endoscopic surveys performed in high-risk groups from different countries have demonstrated the presence of chronic oesophagitis in 42–84 per cent, atrophy in 3·8–10·8 per cent, and dysplasia in 2·4–8 per cent[16–18]. These results suggest that the natural history of oesophageal cancer may start with oesophagitis which, in a few individuals, progresses to atrophy and dysplasia of the epithelium and finally to neoplasia[18].

Aetiology

No single environmental factor can account for the pattern of oesophageal cancer in all high-incidence areas[4]. Risk factors that have been shown to be associated with oesophageal cancer are listed in *Table 2*. Oesophageal carcinogenesis is a complex multistep process, and certainly has a multifactorial aetiology. Some factors may be important in the initiation of the neoplastic state, whereas others may act in the promotion and progression of the lesion. Most certainly, the development of invasive oesophageal cancer will result from the synergistic actions between some or many of these aetiological factors. Correa[19] postulates that all the stages of oesophageal carcinogenesis require the action of three kinds of carcinogenic force: predisposing forces (vitamin deficiencies, such as those of A, B, C, E, riboflavin and niacin; oesophagitis, with small erosions and ulcerations), mutagens (nitroso compounds, tannin from cigarettes, alcoholic beverages, etc.), and promoters (phorbol esters present in some alcoholic beverages).

Alcohol and tobacco use

The role of tobacco and alcohol abuse in the aetiology of carcinoma of the oesophagus is well established[7–10,20–28]. Consumption of tobacco and alcohol has been shown repeatedly to be the major cause of SCC of the oesophagus. It has been estimated that more than 80 per cent of cases in industrialized countries can be attributed to exposure to these two environmental factors, either singly or jointly[4,14,20,21,25,28,29]. Large prospective cohort studies uniformly report an association between cigarette smoking and risk of SCC. Similar results have been

Table 2 Risk factors for squamous cell carcinoma of the oesophagus

Alcohol, tobacco smoke	
Dietary factors	Nitrosamines (pickled vegetables, daily barbecue, highly salted foods, etc) Micotoxins (*Fusarium*, *Alternaria*, *Geotrichum*, *Aspergillus*) Corn consumption Retinol
Nutritional deficiencies	Vitamins A, C, E, niacin, riboflavin, zinc Low intake of fresh fruit and vegetables
Environmental factors	Low socioeconomic status Soil deficiencies (molybdenum, manganese, zinc) Fibrous silica and water contamination Metal dust (beryllium, chromium, chromates)
Occupational factors	Vulcanization workers Plumbers and pipefitters
Infectious agents	Papillomavirus, fungi, bacteria
Chronic irritation	Thermal and mechanical (spicy and hot foods, mate drinking, rapid eating) Achalasia Chronic lye strictures Oesophageal diverticulum
Radiation therapy	
Injection sclerotherapy	
Genetic predisposition	
Other tumours of the upper aerodigestive tract	
Gastric resection	
Associated diseases	Plummer–Vinson syndrome Coeliac disease Tylosis Scleroderma

Table 3 Case-control studies showing the relative risks of alcohol abuse and tobacco smoke in oesophageal cancer

Reference	Year	Location of study	No. of patients with oesophageal cancer	No. of controls	Relative risk: Alcohol	Relative risk: Tobacco
Pottern *et al.*[8]	1981	Washington DC	120	250	6·4 (2·5–16·4)	1·9 (1·0–3·5)
Yu *et al.*[21]	1988	Los Angeles	275	275	15·5 (5·9–41·1)	11·5 (4·5–29·8)
Ferraroni *et al.*[10]	1989	Italy	209	1944	4·29	19·35
De Stefani *et al*[9]	1990	Uruguay	261	522	5·27 (2·7–10·2)	4·62 (1·9–11·1)
Graham *et al*[22]	1990	New York	178	174	3·07 (1·65–5·71)	2·49 (1·34–4·64)
Franceschi *et al.*[23]	1990	Italy	288	1272	6·0 (3·7–10·0)	3·8 (2·2–6·6)
Sankaranarayanan *et al.*[24]	1991	India	267	895	2·33 (1·52–3·55)	4·8 (2·34–9·83)
Cheng *et al*[26]	1992	Hong Kong	400	1598	11·45 (6·66–19·69)	5·83 (2·83–12·02)

Values in parentheses are 95 per cent confidence intervals obtained from well designed case–control studies (*Table 3*)[8–10,21–24,26]. Furthermore, such studies have shown a dose–response relationship after controlling for possible confounding factors[14,21,28,30].

The lighted cigarette generates about 4000 compounds that can be separated into gas and particulate phases. The major tumorigenic activity of tobacco smoke is contained in the particulate matter, or tar fraction. The primary initiators are presumably the polynuclear aromatic hydrocarbons, such as benzo(a)pyrene and volatile nitrosamines (*Table 4*)[4,9]. Pipe and cigar smokers have a greater risk of cancer of the oral cavity and oesophagus than cigarette smokers[9,20,23,27–29]. It has been proposed that pipe tobacco condensates are swallowed into the oesophagus, allowing close contact of the tobacco carcinogens with the oesophageal mucosa[27,28].

The relative risk of oesophageal cancer in smokers is higher in communities smoking mainly black (air-cured) tobacco than in those using blond (flue-cured) tobacco[9,27]. Black tobacco contains lower levels of polycyclic aromatic hydrocarbon and higher levels of *N*-nitroso compounds than blond tobacco[9,27]. These compounds have been proven to induce oesophageal cancer in rodents under experimental conditions[31]. Also, hand-rolled cigarette smoking, which could be considered an indicator of black tobacco smoking, was also associated with a higher risk of oesophageal cancer, compared with the use of commercial cigarettes[27]. The risk increases with increasing number of cigarettes and duration of the smoking habit[4,8,14,21,28,30,32]. Generally, ex-smokers of cigarettes have a reduced risk relative to those who continue to smoke, and current smokers of two or more packs per day display a higher risk than those who smoke less[4,9,21].

Differential risks for carcinoma of the oesophagus are also observed with different types of alcoholic drink[7 8 20 21]. For any given level of ethanol intake, the risk from spirits is usually more than twice that from beer; the risk from wine is intermediate between that from spirits and that from beer[7,8,20,21,32]. Whatever the type of alcohol consumption, however, there is a highly significant correlation with the average daily dose of ethanol[7,8,20,21,28,30]. The exact mechanism responsible for the increased risk in alcohol drinkers is not known (*Table 4*)[4,33,34].

Table 4 Carcinogenic actions of ethanol and smoking

- Ethanol
  - Direct local action by carcinogens (nitrosamines, oils, polycyclic hydrocarbons, etc.)
  - Interaction with other agents (tobacco)
  - Induction of nutritional deficiencies (riboflavin, nicotinic acid, iron, zinc, etc.)
  - Decreased chemical detoxification and biotransformation due to liver injury
  - Impairment of immune system
- Smoking
  - Direct local action by carcinogens (aromatic hydrocarbons, volute nitrosamines, etc.)
  - Exposure to heated smoke

The importance of either smoking or drinking alone as a single aetiological factor has been questioned, since so many patients who use tobacco also consume alcohol. However, several prospective case–control studies of patients who drink but do not smoke and, conversely, of patients who smoke but do not drink have established convincingly the independent importance of both tobacco and alcohol as carcinogens of the oesophagus (*Table 5*)[28,29,35]. In addition to their effect as independent risk factors, alcohol and tobacco exert a synergistic action by potentiating each other[8,14,28]. Data from a case–control study conducted in Ille-et-Villaine, a high-risk area of France, demonstrated that, while the relative risk for men consuming more than 120 g alcohol daily was 49·6 and the risk associated with smoking more than 30 g tobacco was 7·8, the risk for those who had both addictions was 155·6[36].

Dietary carcinogens

Epidemiological and experimental evidence suggests that nitrosamines are involved in the aetiology of oesophageal carcinoma[31,37]. A high content of nitrosamine in the diet is a particularly important risk factor in some African and Far East countries[6]. Nitrosamines and their precursors (nitrate, nitrite, and secondary amines) were detected in various common foods and drinking water consumed in Linxian County, China, an extremely high-risk area for oesophageal cancer. Moreover, residents of Linxian were found to have significantly higher urinary levels of nitrate and several *N*-nitrosamino acids[11,21,38]. Several studies in China have also shown an association between indices of exposure to *N*-nitroso compounds and death from oesophageal cancer[11]. Chronic oesophagitis is common in young people in Huixian where consumption of pickled vegetables during adolescence is associated with an increased risk of oesophageal cancer[11,26]. Pickled vegetables are known to contain high concentrations of *N*-nitroso compounds[26 39]. This finding strengthens the evidence that *N*-nitroso compounds are carcinogenic in humans and explains partly the very high risk of oesophageal cancer among other Chinese populations[26]. Nitrosamines contained in cured meat products and salted fish have also been considered as carcinogenic agents for oesophageal cancer[6,26,40]. A significant dose–response relationship between intake frequency of fried bacon or

Table 5 Case–control studies showing relative risk of alcohol abuse and tobacco smoke in non-smoking and non-drinking patients respectively

Reference	Year	Location of study	No. of patients with oesophageal cancer*	No. of controls*	Relative risk†	
					Alcohol	Tobacco
Tuyns[28]	1983	France	734	1976	11 04	5 16
La Vecchia and Negri[29]	1989	Italy	250	1089	3·6 (0·9–13·6)	6·2 (1·3–29·9)
Cheng *et al.*[15]	1995	Hong Kong	400	1598	3·18 (1·5–6·7)	10·27 (1·83–57·64)

Values in parentheses are 95 per cent confidence intervals ham and risk of oesophageal carcinoma has been observed[21].

The Kashmir province of India, another high-risk area, is associated with several specific personal and dietary habits[40]. The diet contains substantial amounts of *N*-nitroso compounds. These include salt tea, dried fish, vegetables (especially *Brassica olerecea*), red chillies and spice cake. The dietary habit that is likely to have the greatest risk for SCC of the oesophagus is the consumption of smoked fish and large quantities of hot, salted tea[40]. Drying raw foodstuffs in the open sun under humid conditions provokes high concentrations of *N*-nitroso compounds[40]. A high proportion of households in the high-risk region of Turkoman Sahara also preserve their food by local methods such as sun-drying and salting. Moreover, they tend to store these foods for longer periods than families in moderate- and low-risk regions[41]. A clear increase in risk has also been observed for those eating barbecued food daily compared with those eating it less frequently, even after adjusting for meat consumption[9]. Laboratory investigations showed the presence of animal carcinogens and mutagens in barbecued foods formed by the pyrolysis of proteins[9].

Nutritional deficiencies and dietary risks

Although epidemiological research has linked poor nutrition with cancer in large populations, such studies are inadequate for measuring the relationship between specific dietary deficiencies and risk of disease in relatively homogeneous populations[42]. Most evidence suggests that a chronic low intake of several micronutrients, together with an inadequate protein intake, increases the predisposition of the oesophageal epithelium to neoplastic transformation[33]. Diets deficient in vitamins A, C, E, niacin, riboflavin and zinc have been suggested as risk factors for oesophageal cancer[33,43,44]. Vitamin A and riboflavin deficiencies have long been known to promote hepatic and skin carcinogenesis in certain animal models, and to cause extensive lesions in the oesophageal epithelium of both animals and humans[33,43,44].

Food habits, such as a long-standing simple starchy diet without fresh fruit and vegetables, resulting in nutritional deficiencies, and continuous physical and thermal irritation of the oesophagus may play an important role in the aetiology of SCC[4,6,25,41]. Most studies have found an inverse relationship between fruit and vegetable consumption and risk of oesophageal cancer, although the evidence is less clear in some investigations. Attributing protection to any specific micronutrients is, at present, impossible; beta-carotene, vitamin C and riboflavin have been proposed as possible candidates[1,23,33,45]. Rural Transkeians at high risk of oesophageal cancer were found to have an inadequate intake of calcium, nicotinic acid, riboflavin and ascorbic acid[12].

Case–control studies carried out among black men with oesophageal cancer in Washington DC revealed that they ate more processed and starchy foods and less red meat, chicken, eggs, fruit and vegetables than controls[8,46]. In addition, several studies in Europe have shown significant negative associations between the consumption of fresh meat, vegetables and fruit, and risk of oesophageal cancer[4,23,25]. Zinc levels have been found to be lower in patients with oesophageal cancer than in healthy controls[11]. Experimentally, severe zinc deficiency increases the incidence of methylbenzylnitrosamine-induced oesophageal cancer in rats[47]. A deficiency of nicotinic acid is the outstanding nutritional feature of corn-eating populations[33]. Pellagra emerged as a common disease in Transkei around 1930, a high-risk area for oesophageal cancer[33] . Clinically, patients with pellagra usually have an intensely hyperaemic and sometimes oedematous oesophageal mucosa; others develop secondary ulcerations, constrictions, and dysphagia[33]. Signs of oesophagitis were also found in 80 per cent of individuals among the population of Iran at high risk for oesophageal cancer[16,33]. Foods that provide large amounts of retinol appear to increase the risk of cancer of the oesophagus substantially and in a dose-dependent fashion[22].

A comparison of incidence of oesophageal cancer with dietary staples and composition of foods in 21 low- and 17 high-risk regions in Africa revealed that in the low-risk regions, the dietary staples were either sorghum, millet, cassava, yams or peanuts, or a combination of these food items, whereas in the high-risk areas there was a starchy diet, consisting of corn or wheat, and nutritional deficiencies[6,33]. It is calculated that dietary staples associated with a high risk of oesophageal cancer are deficient in riboflavin, nicotinic acid, magnesium and zinc, whereas dietary staples associated with a low risk of oesophageal cancer are rich in these substances[33].

Environmental factors and pollutants

Environmental factors appear to play a predominant role in oesophageal carcinogenesis. As early as in 1966, Burrell and his associates[48] proposed the soil theory to explain the endemic spread of oesophageal cancer in Transkei, South Africa. Areas of high incidence of this neoplasia were distinguishable from those of low incidence by differences in either the plantation productivity on the ground or the content of molybdenum and other trace elements in the soil[11,48]. High-risk areas were much lower in both the biological and chemical richness of soil than low-risk areas[11,48,49]. The association of suboptimal geochemical environment with an increased cancer risk was also reported in Iran[50], China[51] and Japan[49]. Japan was divided into high-risk and low-risk regions. The ten highest-risk areas and the seven lowest-risk areas were clearly separated by two fault lines of the Japanese islands, a finding suggesting that some microelements of the soil may play a role in conditioning the cancer risk[49]. High-risk areas are either loam lands with a predominance of volcanic ash precipitate or raised sea bottoms covered with a layer of metamorphic rock. Low-risk areas, located along the Fossa Magna Line and the Median Line, are associated with an abundance of granite rock penetration from the rock magna. There is an inverse correlation between mortality rate from oesophageal cancer and soil content of molybdenum, manganese, zinc, magnesium, silicon, nickel, iron, bromium, iodine, chlorine, potassium, sodium, phosphorus and bicarbonate[11]. How these substances affect the oesophageal epithelium is not known but, for example, molybdenum is a co-factor of the enzyme nitrate reductase which affects the nitrite and nitrate content in plants[11,49].

An increased incidence of oesophageal cancer has been linked to petroleum contamination of water in Saudi Arabia[52]. Traces of petroleum oil were found in five of six water samples from Gassim, a high-risk area, compared with three of 49 samples from other areas. Mutagenicity tests on water specimens from Gassim region indicated the presence of possible carcinogens. Concurrent malnutrition, particularly vitamin A deficiency, may further enhance the carcinogenic risk of such pollutants[52].

Some authors have found a significant association between carcinoma of the oesophagus and long-term occupational exposure to metal dust (beryllium, chromium, chromates and nickel)[21]. These metals have been shown to be risk factors for respiratory cancers in humans, lending some credibility to the hypothesis that the observed association between oesophageal cancer and exposure to metal dust is a causal one. A possible occupational hazard in vulcanization workers, plumbers and pipefitters has also been identified[53].

Infective factors

Micro-organisms may also have an aetiological role in oesophageal carcinogenesis either by producing carcinogens or promoters, or by acting directly on host cells[54]. The chronic inflammatory processes caused by infectious micro-organisms may result in sustained regenerative proliferation of cells and increase the risk of cancer development[54]. The striking geographical distribution of oesophageal cancer might represent another example of a malignant tumour with a possible viral aetiology[55,56].

Human papillomaviruses (HPVs) of various DNA types have been strongly implicated in the pathogenesis of cancers that develop in several squamous epithelia, including cervix, vulva, larynx and skin[54–56]. In the past decade, HPV infection has also been found in chronic oesophageal irritation, papilloma and oesophageal cancer[54–62]. HPV infection of the oesophagus was suggested by morphological studies showing HPV-induced cytopathic changes, and confirmed by immunohistochemical techniques demonstrating HPV antigens in squamous cell papillomas[55,57,60]. Subsequently, DNA hybridization studies and polymerase chain reaction techniques disclosed HPV DNA sequences in both benign and malignant oesophageal lesions[58,60,62]. HPV is particularly prevalent in high-risk populations in China and in patients with cytological evidence of precancerous lesions. HPV was found in 22·0 per cent of patients without cytologic atypia, 50·0 per cent with mild dysplasia, 80·6 per cent with moderate dysplasia, 67·9 per cent with severe dysplasia and 66·7 per cent with invasive SCC[56]. Additionally, *in vitro* and *in vivo* experimental studies have confirmed the oncogenic properties of HPV types 16 and 18[62,63]. Protein of HPV types 16 and 18 E6 binds to the tumour-suppressor protein p53 and promotes its degradation[64].

Fungi have also been implicated as aetiological agents in oesophageal cancer[54]. In areas where oesophageal cancer is prevalent, grains and foodstuffs are frequently contaminated with fungi. Studies in the high-risk areas for oesophageal cancer in China showed that some common species of fungus, belonging to the genera *Fusarium*, *Alternaria*, *Geotrichum*, *Aspergillus*, *Cladosporium* and *Penicillium*, are frequently detected in grain[11,51,65,66]. Such fungi can not only reduce nitrates to nitrites but also decompose proteins and increase the amount of amines in food, consequently promoting the formation of nitrosamines. Maize grown in poor soil with zinc and molybdenum deficiencies has been identified in the high-risk areas for SCC of the oesophagus[67,68]. Molybdenum deficiency increases the susceptibility of maize to a variety of fungal species, especially *Fusarium* and *Aspergillus*, which are capable of producing carcinogenic metabolites[38,54]. Of the various infections of the oesophagus, fungal infections, particularly those of *Candida* species, are by far the most common[54,69]. The presence of fungus, as determined by cytological analysis, correlates with the degree of dysplasia. Oesophageal fungus was found in 31 per cent of normal subjects and those with mild dysplasia, in 72 per cent of those with severe dysplasia, and in 90 per cent of those with oesophageal cancer[11,54].

Bacteria are normally present in the upper alimentary tract, including the oesophagus. In the human oral cavity, nitrates are partially (20 per cent) converted into nitrites by the oral microflora[54,70]. Deregulation of the normal flora may increase the production of these compounds. Extremely high concentrations of nitrates and nitrites were detected in gastric juice and saliva in Linxian inhabitants[54]. Salivary nitrates in patients with marked epithelial dysplasia or oesophageal cancer were significantly higher than in normal controls[54].

Chronic oesophageal irritation

Thermal and mechanical irritation. Chronic chemical and/or physical irritation of the oesophageal mucosa is frequently reported by patients who develop oesophageal cancer. Ingestion of extremely hot beverages has been shown to increase the risk of oesophageal cancer in Puerto Rico[32], Singapore[71], Iran[72], Uruguay[9], Brazil[73], India[40], China[11,54] and Japan[13]. Opium smoking has been implicated in oesophageal cancer in high-risk areas of Iran and China[72], while ingestion of betel nuts is a frequent habit of inhabitants of Sri Lanka[74]. Several studies have observed an association between drinking of the plant extract mate and precancerous and SCC of the upper digestive tract[9,73,75]. The drinking of mate is a common habit in parts of southeastern South America where the gaucho culture is widespread, including Argentina, Uruguay, southern Brazil and Paraguay. These areas, particularly Uruguay and southern Brazil, have high incidences of oesophageal cancer[73]. Two possible mechanisms by which mate drinking might increase the risk of oesophageal cancer include a carcinogenic effect of the plant extract or an increased susceptibility of the oesophagus to carcinogens following thermal injury from hot mate[9].

Fibrous material contaminates the diet in north-east Iran where there is a very high incidence of oesophageal cancer[76]. Examination of the seeds from more than 60 different species of weed known to contaminate the wheat in this area of the Middle East shows that the fibre originates from the seeds of the common Mediterranean grass, *Phalaris minor*. The fibres are broken off from the seed when the wheat is milled but persist in the flour. Experimentally, when cells of the 3T3 mouse fibroblast line are exposed to these fibres in semisolid suspension culture, their proliferation is stimulated more than 100-fold[76].

Irritation of the oesophagus by curry or spicy seasonings has been considered as a possible risk factor in oesophageal cancer[6]. In the USA, a case–control study showed that 35 per cent of patients with oesophageal cancer preferred spicy foods, compared with 21 per cent of controls[20]. A study in Puerto Rico[32] showed that 3 per cent of the patients *versus* 1 per cent of the controls used a large quantity of spices. Part of the traditional diet during pregnancy in the high-risk region of northern Iran is black pepper, which may be related to the high incidence of cancer of the oesophagus among women in northern Iran[6].

Partially chewed food swallowed rapidly may cause continuous physical irritation to the oesophagus. Epidemiological studies have revealed that most patients with oesophageal cancer eat their food very quickly without chewing it well. This is particularly true in northern Iran, where the main food is local bread, which is often hard, scratchy and contains fibrous silica[6].

Achalasia. Achalasia is a motility disorder caused by degeneration of the intrinsic autonomic nerves in the wall of the oesophagus and lower oesophageal sphincter. This results in decreased or absent peristalsis in the smooth muscle portion of the oesophagus and impaired relaxation of the lower oesophageal sphincter[77]. Fagge[78] in 1872 was the first to report oesophageal cancer in patients with achalasia. Although it is generally agreed that oesophageal cancer occurs in those with long-standing achalasia, the true prevalence and incidence of malignant degeneration in achalasia is still a matter of debate[77–96]. Autopsy studies on patients with achalasia in whom oesophageal cancer was detected at post-mortem examination revealed a prevalence of 20–29 per cent[81,83,84]. The prevalence reported in clinical studies of patients with achalasia in whom oesophageal cancer was detected during a follow-up period ranged from 0 to 8·6 per cent (*Table 6*). The duration of follow-up, and both the number and selection of patients, influence the risk of malignant degeneration, which varies from seven-fold to 33-fold[88,92,94–96].

Symptoms of achalasia are present for an average of 15–20 years before the diagnosis of carcinoma is made[87–89]. The tumour usually develops in the dilated portion of the middle and lower thoracic oesophagus[88–90]. It frequently extends for some distance along the oesophagus, is often cauliflower in shape and has a marked tendency to invade by extension through the submucosa[86,90]. Most oesophageal cancer complicating achalasia is SCC, although adenocarcinoma associated with Barrett's oesophagus has been reported following surgical myotomy[77,97]. Reflux and subsequent oesophagitis are common late complications of surgical myotomy for achalasia, occurring in 18–31 per cent of patients[98]. Because of the high incidence of reflux oesophagitis after simple myotomy, many surgeons propose adding an antireflux procedure[98,99].

Carcinoma as a complication of achalasia is rarely found in its early stages because patients with long-standing difficulty in swallowing are likely to attribute any symptomatic change to their original disease[88]. Weight loss and an alteration or recurrence in the pattern of dysphagia are the most common harbingers of malignant change[86,87,89,91]. Blood-stained regurgitation or haematemesis, and retrosternal or back pain are other common symptoms of malignancy[87,90]. Radiographic and endoscopic recognition of the carcinoma can be difficult, because relatively large growths may arise from the wall of a dilated oesophagus filled with fluid and food and so escape detection[89,90]. Proper preparation of the oesophagus is, therefore, an essential part of these diagnostic procedures[88,89]. Because of the delay in diagnosis, the prognosis is extremely poor[88–91,93]. The extent and spread of the growth usually precludes the possibility of a curative procedure. The resectability rate is low, approximately 20 per cent for patients with achalasia and oesophageal cancer[92].

The mechanism responsible for the increased risk of SCC in patients with achalasia is unclear, but it is most likely related to stasis. Guisez[100] in 1921 called attention to the role played by stasis in the malignant transformation in achalasia. It is believed that development of the tumour is related to prolonged contact of certain elements of often partially degraded ingested food with the oesophageal mucosa; these result in increased bacterial growth and chemical irritation that culminates in chronic oesophagitis[88,93]. Endoscopy usually reveals a hyperaemic mucosa, irritation and spasm. Biopsy at this stage will demonstrate infiltration by inflammatory cells[86]. Thus, it is conceivable that early treatment to relieve retention may reduce the risk of oesophageal cancer; late operation on a dilated oesophagus does not prevent the development of cancer[87,89]. The incidence of tumour in patients with achalasia according to the treatment employed (no treatment, pneumatic dilatation, myotomy) has been studied. SCC occurs eight times more frequently in untreated patients with achalasia and 4·5 times more often in patients treated by pneumatic dilatation than in those having surgical myotomy[94].

According to studies of cell growth kinetics and data from mass screening programmes, progression from carcinoma *in situ* to invasive oesophageal SCC may take 3–4 years[92,101]. Therefore, an endoscopic surveillance programme may be indicated in those with achalasia,

Table 6 Prevalence and incidence of oesophageal cancer in patients with achalasia

Reference	Year	No. of patients with achalasia	No. of patients with cancer	Sex ratio (M:F)	Prevalence (%)	Follow-up (years)	Duration of dysphagia (years)	Incidence (per 100 000)	Risk (fold)
Camara-Lopes[85]	1961	90	7	—	7·7	—	15·5	—	—
Just-Viera and Haight[86]	1969	148	5	—	3·3	—	21·4	—	—
Lortat-Jacob *et al.*[87]	1969	279	24	1·2:1	8·6	—	—	—	—
Wychulis *et al.*[88]	1971	1318	7	6:1	0·5	13	28	41	7
Hankins and McLaughlin[89]	1975	156	2	—	1·3	13	8·5	98	—
Carter and Brewer[90]	1975	60	4	1:1	6·7	—	15·2	—	—
Pinotti *et al.*[91]	1980	308	12	3:1	3·9	7	15	—	—
Chuong *et al.*[79]	1984	100	0	1:1·3	0	6·46	—	—	—
Peracchia *et al.*[81]	1991	244	1	—	0·4	3·7	9	18·6	—
Meijssen *et al.*[92]	1992	195	3	1:1·2	1·5	874 person/years	17	340	33
Aggestrup *et al*[93]	1992	146	10	1·7:1	6·8	23·2	16·7	—	—
Brossard *et al.*[94]	1992	203	13	—	6·4	10	—	—	8
Sandler *et al.*[95]	1995	1062	24	1·1:1	2·3	9864 person/years	1–24	145·9	16
Streitz *et al.*[96]	1995	241	9	2:1	3·7	1138 person/years	—	88	14·5

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especially when there is a history of dysphagia lasting 15 years or more[82,89,92,93]. Further studies are needed to clarify the cost-effectiveness of such surveillance.

Chronic lye strictures. Late complications of acid or lye burns in the oesophagus are cicatricial strictures and the development of carcinoma[5,102,103]. The magnitude of the risk is not definitely known. The incidence of lye corrosion in oesophageal cancer is generally between 0·8 and 5·0 per cent[103–106]. Kiviranta's[105] findings of nine patients with carcinoma in a group of 381 with caustic injuries suggests that the risk of oesophageal cancer is approximately 1000-fold greater than for others in the same age group[103,105,106]. The average age for development of SCC after caustic injury is about 50 years, compared with approximately 60 years for SCC of the oesophagus without previous exposure (*Table 7*)[103,104,106–108]. The time interval from the caustic burn to the onset of carcinoma averages about 40 years[103,104,106–108]. As with primary oesophageal cancer, men are more frequently affected than women[103–106]. The lye stricture is usually found in the area of the tracheal bifurcation and the carcinoma usually develops in the stricture[5,103,104,106–108]. The mechanism by which a caustic burn predisposes the patient to carcinoma is unclear. Experimental studies in rats have demonstrated that oesophageal tumours develop after *N*-ethyl-*N*-butylnitrosamine, most commonly in areas of oesophageal stenosis[109]. This may be equated to other situations of chronic inflammation, such as the increased risk of cancer in achalasia or chronic ulcerative colitis[106].

Appelqvist and Salmo[103] noted a better prognosis for lye corrosion carcinoma compared with ordinary oesophageal cancer. They suggested that patients with lye corrosion carcinoma are younger, obstructive symptoms occur sooner in an already narrowed oesophagus, and the lye stricture is surrounded by scar tissue which prevents early dissemination of the carcinoma[103,106]. Because of the high risk of development of SCC of the oesophagus, regular endoscopic examination including cytological study of endoscopic washings and biopsy should be done[104].

Oesophageal diverticuli. Malignant transformation in a chronic pharyngo-oesophageal or Zenker's diverticulum is rare and most of the reported cases appear in the literature as reports of single cases[110–114]. Of 961 surgical cases of pharyngo-oesophageal diverticula at the Mayo Clinic from 1930 to 1968, three were complicated by carcinoma, an incidence of 0·31 per cent. All patients were over 60 years old and all had had a large pharyngo-oesophageal diverticulum for many years[110,111]. Most authors have speculated that the chronic irritation and inflammation resulting from retained food and secretions in these large pouches are contributing factors in the development of carcinoma[110,111]. The diagnosis is often delayed, which may explain the low long-term survival rate[110]. Consequently, a diverticulum that is large enough to produce symptoms leading to its diagnosis is large enough to warrant operation[110–114].

Irradiation and chemotherapy. Therapeutic irradiation is well known to be associated with an increased risk of neoplasm development in organs within the irradiated field[115–123]. Experimental induction of SCC of the oesophagus in mice has been reported with an incidence related to the intensity of the radiation administered[119]. The number of reported cases of SCC of oesophagus following irradiation is anecdotal[115–118,120–122]. It is sometimes doubtful whether a carcinoma arising within a previously irradiated organ is due to radiation or whether it constitutes a second primary cancer unrelated to radiotherapy[117,118]. Criteria suggesting the diagnosis of radiation-induced malignancy are: (1) a previous history of irradiation; (2) appearance within the irradiated field; (3) observable chronic radiation damage; and (4) a long interval between exposure to radiation and development of the malignancy. The latter two criteria are not regarded as absolute[121,123].

The effects of radiation appear to differ according to age at the time of exposure, dose, duration of radiation and the tissue irradiated. Chemotherapeutic agents have also been known to cause certain tumours[120–124]. Systemic therapy may confound the radiation-induced cellular injury or interfere with cellular repair mechanisms. It is possible that the incidence of a second neoplasm represents a carcinogenic effect superimposed upon a susceptible patient.

The initial disease can be divided into benign and malignant conditions, including thyroid disease, tuberculous adenitis, breast cancer, lymphoma, laryngeal cancer, carcinoma of the testis and others[115,116,121,122]. The dose ranges from 26 to 100 (mean 46·8) Gy[115,117,120]. There is no obvious correlation between dose and latency[117]. The latent period between initial radiation therapy and diagnosis of oesophageal cancer ranges from 3 to 56 (mean 25) years and is significantly shorter in patients who received irradiation for malignant disease[117,118]. Women are more frequently affected than men and the predominant histological type is SCC; few cases of adenocarcinoma, fibrosarcoma and leiomyosarcoma have been reported[115–122]. Vigilant follow-up of patients with previous mediastinal irradiation is essential for early recognition and prompt treatment of subsequent SCC of the oesophagus[118,121].

Injection sclerotherapy. Endoscopic injection sclerotherapy has been widely used for treatment of bleeding oesophageal varices. Several isolated cases of oesophageal cancer following endoscopic sclerotherapy have been reported[125–127]. The middle and lower third of the oesophagus are the preferential sites for development of

Table 7 Clinical characteristics of patients who developed oesophageal cancer following caustic injury in reported series

Reference	Year	No. of patients	Mean age (years)	Interval since caustic injury (years)	Site of tumour			Resectability (%)
					Upper	Middle	Lower	
Bigelow[107]	1953	10	35	31·2	—	—	—	10
Imre and Kopp[108]	1972	10	52	40·5	2	6	2	50
Appelqvist and Salmo[103]	1980	63	48	41·5	5	53	5	83
Hopkins and Postlethwait[106]	1981	12	53	45·8	2	9	1	75
Isolauri and Markkula[104]	1989	15	57	52·5	0	14	1	67

tumours and the majority are SCC[125]. Prognosis is generally poor because of advanced carcinoma and accompanying liver dysfunction[125]. Some authors believe that the relationship between sclerotherapy and oesophageal carcinoma is fortuitous, emphasizing a causal association with other risk factors such as age, alcohol–tobacco intoxication, or Barrett's oesophagus[127].

Genetic predisposition

Although ethnicity is a strong indicator of risk for this disease, no specific genetic factor has been identified[5]. Because ethnic groups tend to share similarities in diet and geography, the identification of specific population-based genetic risk is difficult. There are several reports, however, that indicate an increased incidence among blood relatives[128,129]. The frequency of oesophageal cancer varies among the native and immigrant populations in different countries. A follow-up survey of 622 families with a history of oesophageal cancer was carried out in Yangcheng County, China, totalling 5037 families[130]. During a 10-year period, 35·8 per cent of new deaths were found in families that previously had two or more deaths due to oesophageal cancer, which accounted for only 7·8 per cent of the total families. Offspring from households where one or both parents died from oesophageal cancer also showed a higher mortality from the same disease[130]. These results point to a strong tendency of familial aggregation of oesophageal cancer and the existence of genetically determined susceptibility.

Second primary tumour

SCC of the oesophagus is also frequently associated with other synchronous or metachronous tumours in the upper aerodigestive tract[131–151]. The incidence of multiple primary SCC of the aerodigestive tract ranges from 3·7 to to 30 per cent[131–151]. Crude rates below 11 per cent have been reported in studies with a relatively short follow-up. This wide range in incidence may be explained partially by the site of the index tumour, type of treatment, ethnic and racial differences, increased life expectancy, and partially by the increasing awareness of such tumours, leading to more prompt evaluation and improved survival rates associated with the initial primary lesion[137,138,142,148]. These multiple neoplasms are highly selective on a site-specific basis, presumably because of common aetiological factors associated with the initial cancer.

The risk may be directly proportional to the amount and duration of exposure to carcinogens. Moore[149] found that 40 per cent of patients with index cancers of the oral cavity, pharynx and larynx, who continued to smoke developed a second primary tumour, while only 6 per cent who stopped smoking after onset of the first lesion did so. The time necessary to develop the second tumour is dependent on several factors, one of which is the survival time following treatment of the index tumour[148]. The risk of developing a second primary cancer is enhanced significantly by more intensive, combined exposure to tobacco and alcohol before identification of the index cancer[147,150]. When comparing former with current cigarette smokers, prospective studies have generally indicated a 25–50 per cent reduction in the risk of cancer of the oral cavity and larynx by cessation of smoking[147–150].

The field effect theory has been advanced to explain these so-called synchronous and metachronous carcinomas[131]. This model predicts that independent tumours will develop from the genotoxic effects of carcinogen shared by many cells in the field. The entire mucosa of the upper aerodigestive tract, when exposed to such local irritants as tobacco, smoke and alcohol, is at risk of developing cancer. According to this theory, areas of atypical epithelial hyperplasia, metaplasia, dysplasia, preinvasive carcinoma (*in situ*) and fully developed carcinoma may be found at various sites in the upper aerodigestive tract. The present authors studied 17 patients with multiple primary tumours of the upper aerodigestive tract for the presence and genotype of p53 gene mutations. The results showed a complete discordance in p53 genotype between separate primary tumours and, therefore, favour the field effect theory[151]. Because of the clear risk for metachronous cancers, it is recommended that all patients with tumours of the upper aerodigestive tract undergo close medical follow-up over a long period of time. This should allow early detection of second primary cancers, especially tobacco-related lesions[135,136,146].

Gastric surgery

There is some controversy regarding the increased relative risk of oesophageal cancer in patients who have undergone gastrectomy for benign conditions. Increased risk was reported from several cohort and case–control studies with large numbers of patients[152–155], but this has not been supported by other reports[156]. Gastrectomy may cause gastric hypoacidity and favour oesophageal reflux, leading to development of Barrett's oesophagus and adenocarcinoma of the oesophagus. An increased relative risk was observed for cancer of the colon and rectum, biliary tract, female breast, pancreas, oesophagus, bladder and lung 20 years or more after gastric surgery[152–155]. These findings suggested that the gastric stump may produce circulating carcinogens such as *N*-nitroso compounds, related to bacterial overgrowth. Some compounds in this class of chemicals are locally acting carcinogens, for example *N*-nitrosamides, while others, such as *N*-nitrosamines, require metabolic activation before the carcinogen is produced[153,154].

Associated diseases

Plummer–Vinson syndrome. Plummer–Vinson syndrome results from a complex deficiency of vitamins (lactoflavin and nicotinamide) and iron[157]. Patients present with atrophy of the oral, pharyngeal and oesophageal mucosa, hypochromatic anaemia and other symptoms. There is frequent occurrence of functional spasms of the oesophagus and cardia which can lead to dysphagia (sideropenic dysphagia). The patients are almost always women, usually between 15 and 50 years of age. They often give a history of weakness and anaemia of many years' duration. The lips are thin and the opening of the mouth is small and inelastic[5,157,158]. There is an increased predisposition to the development of carcinoma of the upper alimentary tract, especially in the mouth, upper part of the oesophagus and hypopharynx. Approximately 10 per cent of patients with this syndrome develop oesophageal or pharyngeal cancer[5,157,158].

Coeliac disease. Patients with either adult coeliac disease or idiopathic steatorrhoea are at increased risk for development of malignant lymphoma and gastrointestinal carcinoma, although the magnitude of this risk is not yet clear[159–162]. Malignancy develops more commonly in men than in women. Although some authors suggested initially that the risk of malignancy may be reduced by adherence to a gluten-free diet, further analysis is required to support this finding[160,161]. When oesophageal cancer develops, it is of squamous cell origin in all cases; two-thirds of lesions are identified in the middle and one-third in the lower oesophagus[161]. The mean age at the time of diagnosis of coeliac disease is 50 years. The interval from the onset of symptoms of coeliac disease to the development of malignancy varies from 15 to 30 years[159–162]. The basis of the association between coeliac disease and gastrointestinal carcinoma is unknown. The nutritional deficiencies that are frequently present in these individuals have been proposed as important factors.

Tylosis. This disease is a hereditary autosomal dominant dyskeratosis, which is characterized by severe epithelial thickening of the hollows of the hands and soles of the feet, and multiple oesophageal papillomas. It has a 95 per cent risk of development of oesophageal cancer after the sixth decade of life[5,163].

Scleroderma. Oesophageal involvement occurs in 70 per cent of patients with scleroderma[164,165]. Reports of several isolated cases of oesophageal cancer associated with scleroderma have raised the possibility of an increased risk of cancer in these patients. The duration of scleroderma before the diagnosis of oesophageal cancer is generally over 10 years and most of the carcinomas are of squamous cell type[166]. The reported prognosis is very poor, with an expected survival of less than 6 months after diagnosis[164,165]. Recently, cases of adenocarcinoma have also been described[167] . It has been speculated that such adenocarcinomas develop as a complication of a Barrett's epithelium. Gastro-oesophageal reflux and peptic oesophagitis may result from a weakened lower oesophageal sphincter and delayed gastric emptying[168].

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British Journal of Surgery 1996, 83, 1186–1196

Review

Sepsis and fat metabolism

J. S. SAMRA, L. K. M. SUMMERS and K. N. FRAYN

Oxford Lipid Metabolism Group, Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford OX2 6HE, UK
Correspondence to: Dr K. N. Frayn

Sepsis is a common surgical problem which can induce profound changes in the plasma concentrations of cytokines and hormones, leading to a catabolic state. Hypertriglyceridaemia and increased fat oxidation are the main features of altered fat metabolism encountered in this state. The endogenous catabolism of sepsis can be reduced by administering exogenous lipid emulsions as a source of metabolic fuel, although the changes in lipid metabolism associated with sepsis may affect the handling of these exogenous lipids. An exciting area for future research is an examination of the ability of lipid emulsions to reduce the morbidity and mortality associated with sepsis by altering immune responses, in addition to limiting catabolism.

Septicaemia is a major cause of morbidity and mortality among critically ill patients[1]. In the United States alone, the incidence of septic shock is 200 000 per annum[2] and in 40 per cent of these cases Gram-negative organisms are the cause[3]. Lipid metabolism is altered in septic shock; Gram-negative septicaemia can induce profound changes[4–6] (*Table 1*). Some abnormalities result from failure of specific organs, while others are part of a host response. Increasingly, artificial nutrition is used to meet the raised metabolic fuel demands in affected individuals, and lipids have become an important source of this fuel. The regulation of lipid metabolism in the patient with sepsis is complex and still unclear. In this review an attempt is made to elucidate the mechanisms influencing this regulation, the consequences for the host and the relevance in terms of nutritional support.

Sepsis and endotoxaemia

The human colon is a common source of Gram-negative septicaemia[3,9] because of its large bacterial content[10,11]. Normally bacteria are kept in the bowel lumen by a mucosal layer which acts as a defensive barrier. This barrier may be damaged as a result of inflammatory bowel disease[12–14], haemorrhagic shock[15–17], trauma[18] or reperfusion injury[19]. The damaged mucosa leads to increased permeability to bacteria and toxins[20]. Most of the bacteria entering the lymphatic system are phagocytosed locally by the reticuloendothelial system and those entering the portal circulation are dealt with by Kupffer cells. The urinary tract[21] and the upper gastrointestinal tract[22] are also significant sources of bacteraemia. When Gram-negative bacteria are phagocytosed their cell wall components may be released into the circulation, resulting in endotoxaemia. However, it is not uncommon to find endotoxaemia in the absence of Gram-negative bacteraemia[23–25]. In 30 per cent of cases the source of sepsis cannot be identified[26].

Endotoxaemia and cytokines

In experimental studies both humans and baboons produce a number of cytokines when challenged with endotoxin[27–29]. Important among these are tumour necrosis factor (TNF) α, interleukin (IL) 1 (α and β) and IL-6. Their appearance in the plasma has a well defined temporal relationship indicative of a ‘cytokine cascade’. TNF appears to be the first factor in this cascade (it is the first to appear), followed by IL-1 and IL-6[30]. Cytokines are important mediators of septic shock, having a pivotal role in regulating host response to sepsis[31–34]. Some cytokines can be detected only in septic shock, whereas others show a marked increase in plasma concentration during sepsis[25,35,36]. The correlation between mortality rate and cytokine levels in these patients is not always clear-cut[37]. Some cytokines (TNF-α, IL-1α and IL-1β) are thought to be produced in paracrine fashion[38], and so their plasma levels may not correlate with their action, while others (IL-6) have a more systemic function[39]. Most cytokines

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Paper accepted 27 March 1996

Table 1 Effect of sepsis on lipid metabolism as shown by the concentrations of glycerol, non-esterified fatty acids and triacylglycerol, and the rate of appearance of glycerol and non-esterified fatty acids

	Plasma glycerol concentration (μmol l⁻¹)[7]	Rate of appearance of glycerol (μmol kg⁻¹ min⁻¹)[8]	Plasma NEFA concentration (μmol l⁻¹)[5]	Rate of appearance of NEFA (μmol kg⁻¹ min⁻¹)[8]	Plasma TAG concentration (μmol l⁻¹)[5]
Normal subjects	70(4) ($n = 16$)	2·4(0·2) ($n = 5$)	970(270) ($n = 5$)	6·5(0·8) ($n = 5$)	1250(100) ($n = 5$)
Patients with sepsis	130(22) ($n = 7$)	6·3(1·1) ($n = 12$)	6450(1600) ($n = 13$)	13·1(3·0) ($n = 12$)	5020(970) ($n = 13$)

Values are mean(s.e.m.). NEFA, non-esterified fatty acid; TAG, triacylglycerol have their own individual receptors, which are normally located on the cell membrane[40]. Cytokines bind to the extracellular domain of their receptor and activate intracellular tyrosine kinases. Once the signal is initiated, the cytokine with its extracellular component of receptor dissociates and forms a soluble complex, which can be detected in the plasma. Some cytokines can modulate their activity through their plasma antagonists[41–44]. The distal members of the cytokine pathway can downregulate the activity of the more proximal members[45], either directly[28,46] or indirectly via hormones[30,47–50].

Over the past few years there has been a rapid expansion in the field of cytokine analysis and currently well over 50 cytokines can be detected in plasma. However, the exact role of these newly discovered cytokines remains to be defined. It is likely that at least some of them will exert an effect on lipid metabolism, either through the hypothalamic–pituitary–adrenal hormone axis[47,51–53] or by altering the haemodynamics of various tissues that participate in lipid metabolism[54,55].

Tumour necrosis factor α

TNF-α is produced by a number of different cells including monocytes, macrophages and adipocytes[56]. It is a peptide (17 kDa) and in plasma exists as a trimer[57]. Lipopolysaccharide of Gram-negative bacteria is the most potent stimulator of its production but viral, fungal and parasitic infections can also act as stimulators[58]. It exerts its effect by binding to specific receptors[59] that activate tyrosine kinase[40]. It has profound metabolic effects, some mediated by hormones, others more directly[28,60,61]. In addition, it can stimulate the production of other cytokines (IL-1, IL-6 and IL-8).

Interleukin 1

There are three distinct species of IL-1 (IL-1α, IL-1β and IL-1 antagonist). They are produced by activated mononuclear phagocytes either under the influence of lipopolysaccharide or TNF. They can directly affect various tissues by binding to cell surface receptors[32]. They can influence the production of other cytokines and can also increase the plasma concentrations of adrenocorticotrophic hormone, cortisol, adrenaline, noradrenaline and glucagon[30,52,53,62].

Regulation of fat metabolism in healthy adults

Adipose tissue stores metabolic fuel in the form of triacylglycerol (TAG). This is by far the largest store of energy as up to a quarter of body-weight can be adipose tissue[63]. A TAG molecule is made up of three fatty acids attached to a glycerol backbone.

After a meal containing fat, TAG molecules are assembled in the enterocytes and extruded as part of a lipoprotein particle (chylomicron–TAG). When these particles pass through the adipose tissue capillaries their TAG content is hydrolysed by lipoprotein lipase (LPL), thereby releasing fatty acids which may be stored in the adipose tissue[64]. In the late postprandial period part of this stored fuel needs to be mobilized. To achieve this an intracellular lipase, hormone-sensitive lipase (HSL), becomes increasingly active. In the adipose tissue the stored TAG is hydrolysed by HSL to produce non-esterified fatty acids (NEFAs) and glycerol[65]. These NEFAs are released into the general circulation from where they are extracted by either the liver or the muscle. In liver, NEFAs are either oxidized or re-esterified to produce TAG. TAG is repackaged with very low density lipoprotein (VLDL) into VLDL–TAG particles, before being released into the general circulation. This VLDL–TAG is hydrolysed in the muscle capillaries by LPL to yield more fatty acids. All these fatty acids are either oxidized directly[66] or stored in the muscle TAG pool[67]. Adipose tissue LPL activity is regulated by plasma insulin levels[68] and is reciprocally linked to muscle LPL activity[69,70]. Adipose tissue HSL activity is inhibited by insulin and stimulated by catecholamines, cortisol and growth hormone[71]. The pathways for mobilization and deposition of fat are summarized in *Fig. 1*.

Fat metabolism in sepsis

The pattern of responses to noxious stimuli has been well defined in terms of ebb and flow phases[72], but in sepsis these phases are less clearly defined[73,74] and so their impact on metabolism is more complex. Fat is the preferred fuel for oxidation in patients with sepsis[8,75,76] and this oxidation cannot be suppressed to the same level with glucose infusion as it can in healthy subjects[77–79]. The high resting energy expenditure in sepsis is accompanied by increased NEFA and glycerol turnover[79,80]. One determinant of the rate of fat oxidation is the plasma NEFA concentration which, in turn, is regulated by fat mobilization[81–83]. In patients with sepsis fat mobilization is far greater than fat oxidation[84], implying considerable cycling[85]. Hormonal perturbations alone have not been

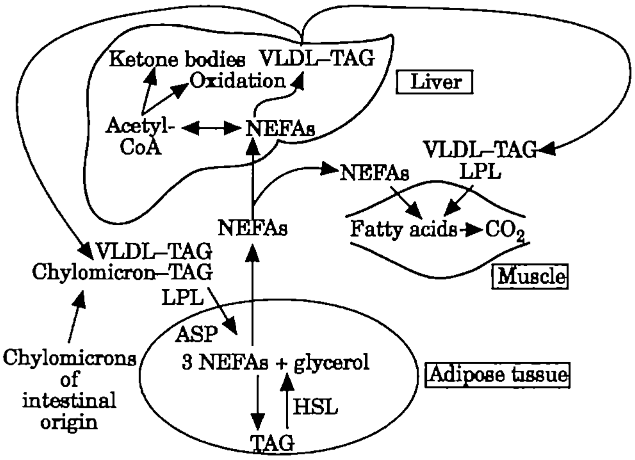

Fig. 1 Normal pathways of lipid metabolism. In the postabsorptive state, lipolysis of triacylglycerol (TAG) stored in the adipose tissue by hormone-sensitive lipase (HSL) yields non-esterified fatty acids (NEFAs). These are removed from plasma by either the muscle or the liver. In the liver, fatty acids can be either oxidized or re-esterified to produce very low density lipoprotein–TAG (VLDL–TAG), which is secreted. VLDL–TAG is hydrolysed by muscle or adipose tissue lipoprotein lipase (LPL) to yield fatty acids, which can be either oxidized in the muscle or stored in the adipose tissue. In the postprandial state dietary TAG in the form of chylomicron–TAG is hydrolysed by the adipose tissue LPL and the fatty acids are directed into the adipose tissue for storage as TAG. This may be reinforced by locally produced acylation-stimulating protein (ASP). CoA, coenzyme A; CO_2, carbon dioxide

able to account for all the metabolic effects seen in sepsis[86,87]; thus the possible role of other mediators was proposed long before the identification and isolation of cytokines[88].

Metabolism of non-esterified fatty acids

NEFAs are released by peripheral adipose tissue to provide metabolic fuel. In patients with sepsis plasma NEFA concentrations are usually raised[5,89], although normal or depressed[90] concentrations have occasionally been observed. Endotoxin challenge to animals results in raised plasma NEFA levels[91,92].

Plasma levels of NEFAs are regulated by lipolysis and adipose tissue blood flow[93]. Endotoxin increases plasma NEFA concentration via its effects on cytokines and hormones. TNF-α is the first cytokine to be released in response to endotoxin; it can increase lipolysis directly[61] as well as indirectly through other hormones[60]. Other cytokines lower down the cascade have been shown to have similar indirect effects, both in animals[94] and humans[62]. Adrenaline[95,96], noradrenaline[97] and cortisol[98] can stimulate lipolysis, thereby increasing plasma NEFA concentrations. Catecholamines can increase adipose tissue blood flow[99 100] and their concentrations in patients with sepsis are raised grossly[101]. Increased plasma ketone body concentrations suppress lipolysis[102] and in sepsis the low levels of ketones may also contribute to increased lipolysis[103]. In patients with sepsis, increased lipolysis and adipose tissue blood flow result in increased plasma NEFA concentration. The increased lipolysis in sepsis depletes the intracellular TAG stores and may contribute to cachexia.

The rate of fat oxidation is determined by the plasma concentration of NEFA[83,92,104]. In sepsis the raised NEFA concentration leads to greater fatty acid oxidation. The low value of respiratory quotient so often seen in patients with sepsis reflects their increased rate of fat oxidation[75].

In some animal models where the insult is particularly severe, low levels of plasma NEFAs have been observed in association with reduced fat oxidation[105]. In these cases adipose tissue perfusion is reduced[106] and less albumin is presented to the adipose tissue, thereby reducing the facility for NEFAs to be transported into the general circulation[107]. A severe reduction in tissue perfusion also leads to anaerobic metabolism and raised lactate levels, which can further suppress lipolysis[108,109].

Metabolism of triacylglycerol

It has long been known that animals injected with bacteria show gross hyperlipidaemia[110,111]. Analysis of lipid fractions has revealed that sepsis can induce hypertriglyceridaemia, mainly through raised VLDL concentrations[91,112,113]. The increase in plasma VLDL–TAG concentration could be due to either increased production by the liver or decreased clearance by peripheral tissue.

Animal studies have shown that the hepatic TAG output can increase by 50 per cent within 2 h of endotoxin challenge[114], and both TNF-α and IL-6 can increase hepatic lipogenesis[98,115]. In humans, hypertriglyceridaemia can be induced in a similar manner by administration of TNF-α or interferon γ[116,117]. This rise in hepatic TAG production is probably mediated by a number of cytokines and hormones, as both anti-TNF and anti-interleukin antibodies fail to suppress endotoxin-induced hypertriglyceridaemia[118,119]. The increased adipose tissue lipolysis in response to endotoxin and cytokines provides increased quantities of fatty acid for TAG synthesis. This rise in plasma NEFA levels alone cannot account for increased hepatic TAG production, as catecholamine-induced lipolysis fails to raise plasma TAG levels. Some animal studies have shown that *de novo* synthesis of fatty acids in the liver is increased after endotoxin administration, but it can still account for only 10 per cent of the TAG of hypertriglyceridaemia[120]. In humans *de novo* synthesis of fatty acids in liver can account for only 1–2 per cent of VLDL–TAG production[121] and its role in sepsis is probably insignificant. It is more likely that during sepsis most of the fatty acids in liver are re-esterified, rather than oxidized, resulting in increased VLDL–TAG synthesis[122].

Plasma VLDL levels can also be increased because of impaired clearance due to reduction in LPL activity. Both muscle and adipose tissue biopsies taken from patients with sepsis have shown reduced LPL activity[68], and animals with sepsis show decreased TAG clearance when exogenous lipid is infused[91,123]. *In vitro* studies have shown that TNF-α, also known as cachectin, is able to suppress LPL activity in adipocyte (3T3-L1) cell lines[124] and subsequently it has become clear that endotoxin can suppress LPL activity through TNF-α production[125,126]. Further studies showed that vascular endothelium was essential for LPL suppression by TNF-α[127], as TNF-α failed to alter LPL activity in isolated adipocytes despite the fact that TNF-α was bound to cell surface receptors[128]. The reduction in the LPL activity in patients with sepsis might imply reduced lipid clearance, but exogenous lipid infusion studies have indicated increased lipid clearance[129]. One possible explanation is that in patients with sepsis tissue blood flow is increased; thus, despite low LPL activity, lipid clearance by adipose and muscle tissue is increased. LPL action is dependent on the type of tissue as well as the nutritional state of the individual[130–132]. The most likely explanation is that the hypertriglyceridaemia of sepsis is caused by a combination of increased TAG production by the liver and decreased VLDL clearance by the peripheral tissue, as summarized in *Fig. 2*.

Adipocytes are capable of producing TNF-α and it has been proposed that they regulate their own mass through TNF-α-induced changes in LPL activity[56,133,134]. This hypothesis of autoregulation has been strengthened by the fact that obese subjects exhibit higher levels of TNF-α messenger RNA in adipose tissue[135]. It is likely that during endotoxaemia this autoregulation breaks down, resulting in loss of fat mass. In patients with sepsis the action of cytokines and hormones on adipose tissue can deplete intracellular TAG stores. In addition, there is a further failure to replenish these stores. The levels of C3a-des-arg, also known as acylation-stimulating protein (ASP), are reduced in sepsis as a result of activation of coagulation and complement pathways[136,137]. ASP acts in concert with adipose tissue LPL to direct fatty acids to esterification and storage[138,139]. Hence, in sepsis the mechanism of fatty acid uptake is impaired and, in addition, the amount of fatty acid available for uptake by the adipose tissue is reduced because of low LPL activity[68,125].

Ketone bodies

Ketone bodies are produced from the oxidation of NEFAs in the liver as an alternative form of metabolic

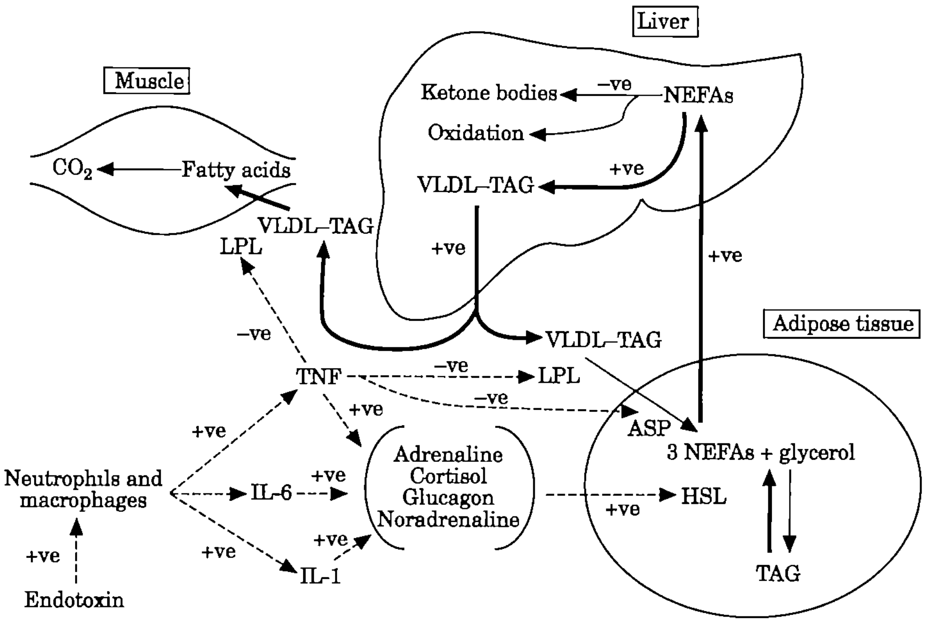

Fig. 2 Effect of sepsis on lipid metabolism. In the liver most fatty acids are re-esterified rather than oxidized. The increased amounts of very low density lipoprotein (VLDL) generated by the liver are poorly cleared by the peripheral tissues because lipoprotein lipase (LPL) activity is reduced by tumour necrosis factor (TNF). In addition VLDL–triacylglycerol(TAG) production may be raised because of increased lipolysis in adipose tissue. Dashed arrows show regulatory pathways. CO_2, carbon dioxide; NEFAs, non-esterified fatty acids; HSL, hormone-sensitive lipase; ASP, acylation-stimulating protein

fuel. In liver, fatty acids are either esterified into TAG or they undergo β-oxidation to yield acetyl coenzyme A (CoA), which can be either completely oxidized or converted into ketone bodies by the hydroxymethylglutaryl–CoA pathway. In starvation, as the plasma NEFA concentration rises, there is increased conversion of NEFAs into ketone bodies[140]. Hormones that stimulate lipolysis also increase plasma ketone body concentrations. However, in sepsis ketone body production is suppressed, despite raised glucagon, cortisol and catecholamine concentrations[141,142], and its suppression cannot be explained by the increased plasma insulin levels alone[143]. Animal studies have shown that both TNF-α and IL-1 can suppress plasma ketone body concentrations in a similar manner to endotoxin[144]. This antiketotic effect of cytokines is likely to be direct, as they increase plasma levels of lipolytic hormones, which would increase plasma NEFA concentrations. The most likely explanation for the suppression of ketone body concentration in sepsis is that fatty acids undergo esterification in the liver (to produce TAG), rather than β-oxidation. An important difference between sepsis and starvation is that in the former plasma TAG levels are raised and in the latter ketone body levels are increased.

Role of hypertriglyceridaemia in sepsis

It is thought that hypertriglyceridaemia is a protective response initiated by the host to counter various biological assaults, in addition to providing a readily available source of energy[145]. It is well known that lipids can bind endotoxin and thereby render it ineffective[146–148]. Most lipoproteins can bind to endotoxin in proportion to their concentration in plasma, and such complexes appear to be stable[149]. More detailed animal studies have revealed that endotoxin becomes an integral part of VLDL *in vivo*, whereas the other lipoproteins are simply bound to it[150]. Although lipoproteins have been shown to have a protective effect against endotoxins in *in vitro* studies, the only study in which hyperlipidaemia was induced with simultaneous endotoxin administration in humans showed that the systemic inflammatory response was potentiated[151].

Exogenous lipids in the nutritional management of patients with sepsis

The increased metabolic fuel demand of patients with sepsis can be met by fatty acids derived from exogenous lipid emulsions[129,152,153]. The major advantage of lipid emulsions over alternative sources of metabolic fuel is their high energy content and low osmolarity. They have a similar effect to glucose in reducing nitrogen loss[84,154–156], but without the added effect of carbon dioxide overload[157]. Lipid emulsions can also alter the phospholipid composition of the cell membranes[158,159], thereby modifying their behaviour.

However, lipid emulsion can exacerbate the hypertriglyceridaemia of sepsis and can lead to even higher concentrations of plasma NEFAs. The hypertriglyceridaemia can interfere with reticuloendothelial[160–162] and pulmonary[163–165] function. Myocardial function can be depressed by hypertriglyceridaemia[166] and the high concentrations of plasma NEFAs can potentially lead to cardiac arrhythmias[167]. The factors that lead to hepatic dysfunction in sepsis are poorly understood[168,169] but balanced nutrition, which includes lipid, can be safely given to patients with hepatocellular damage[170,171].

Lipids can be administered on their own or in combination with glucose and amino acids. If the intake of a substrate exceeds its oxidation capacity, the substrate will accumulate and may cause adverse effects. In practice, the contribution of lipids to the non-protein energy intake should be 30–60 per cent, as excessive lipid administration (i.e. greater than 70 per cent of total energy expenditure) results in increased fat storage[172]. Excessive energy input should be avoided as it has little added effect on nitrogen balance[80,173] and can lead to increased mortality in sepsis[174–177]. Mortality and morbidity rates can potentially be improved in patients with sepsis by providing them with the optimum amount of energy, and maximum benefit can be achieved by combination of different nutrients.

Enteral versus *parenteral*

Lipids can be administered parenterally or enterally; in general the enteral route is associated with fewer complications[178–182]. The main advantage of enteral nutrition is the presence of nutrients within the gut lumen, which is essential for maintaining the gut barrier and immune competence[183,184]. It can also reduce the risk of secondary sepsis in injured patients[180,185] by preventing the overgrowth of gut bacteria[186]. In sepsis, impaired gut mucosal blood flow leads to a reduction in nutrient absorption capacity[187–189]. This can potentially be restored by early enteral nutrition[190]. However, in patients with sepsis the route of nutrient administration may not prevent multiorgan failure[191]. In some patients enteral nutrition may be of only limited use because of primary gut dysfunction.

The main advantage of parenteral nutrition is that it can be given in the presence of gut dysfunction. In addition, the nutrient and energy input can be varied and tightly regulated. However, parenteral nutrition can lead to a severe form of cholestatic jaundice[192,193] and mucosal atrophy[194]. Mucosal atrophy can lead to amplified cytokine and hormonal response during secondary sepsis[195].

The major advantage of lipid solutions is their low osmolarity, allowing them to be administered by a peripheral rather than a central route[196]; this reduces complications associated with central venous nutrition[197,198]. Parenterally administered lipids behave in a similar manner to endogenous lipid because of their ability to acquire apolipoproteins rapidly[199,200]. Finally, the route of nutrition administration in a particular patient with sepsis should depend not only on clinical features but also on available resources.

Long versus *medium-chain triglycerides and selective fatty acids*

TAG is the main lipid constituent of exogenously administered lipid emulsions. Traditionally, the TAG of most lipid solutions contained long-chain (C_{16}–C_{18}) triglycerides (LCTs), but in recent years a number of preparations have become available with medium-chain (C_8–C_{10}) triglycerides (MCTs). Medium-chain fatty acids are more rapidly oxidized than long-chain fatty acids[201,202] because they do not require specific transport mechanisms to enter mitochondria for oxidation.

The metabolic response appears to be different when a combination of MCTs and LCTs is administered rather than LCTs alone. The MCT–LCT combination leads to greater plasma levels of NEFAs and glycerol, as well as an increased plasma insulin concentration[203,204]. Medium-chain fatty acids cannot be re-esterified in the liver; therefore MCT solutions produce a greater ketone body response[205,207] and this can have an additional nitrogen-sparing effect[208,209]. The greater protein-sparing role of MCT has been demonstrated in surgical patients[210], but other studies have shown no clear advantage[155,211].

The intermittent administration of LCTs can lead to impaired reticuloendothelial function and this can be prevented with the use of MCTs[162]. Therefore, the reduction seen in immunological function is smaller with MCT use than with LCT[212,213]. The combination of MCTs and LCTs can reduce the incidence of cholestatic jaundice associated with parenteral nutrition[214]. The medium-chain fatty acids have a trophic effect on the proximal jejunal mucosa, whereas long-chain fatty acids have their effect on the middle part of the jejunal mucosa[215]. Thus a combination of MCTs and LCTs can be used to maximize the trophic effect. In addition, medium-chain fatty acids can reduce bile output, and so can reduce the cathartic effect of bile acids on the colon, preventing diarrhoea[216]. Recently, structured TAGs have become available for clinical use[217]. In these, TAGs are composed of a mixture of medium- and long-chain fatty acids. The theoretical advantage of these structured TAGs over the MCT–LCT combination emulsions is slow and sustained release of medium-chain fatty acids.

Fatty acids play an important role in regulation of the immune response. The plasma profile of fatty acids reflects the composition of exogenously administered lipids[218]. As a result, the immune response can be manipulated by varying the composition of different fatty acids in the lipid solution. A number of *in vivo* studies have shown that *n*-3 polyunsaturated fatty acids are potent inhibitors of lymphocyte proliferation[219,220]. *In vitro* studies have confirmed, in healthy volunteers, that the cytokine response to endotoxin can be modified by *n*-3 fatty acids[221–224]. Dietary manipulation of fatty acids has led to changes in the survival of septic animals[224] and clinical studies have shown that *n*-3 fatty acid administration can lead to a reduced hospital stay[225]. Manipulation of the *n*-3 : *n*-6 fatty acid ratio can lead to amplification or suppression of the immune response[226]. It seems possible that morbidity and mortality rates in patients with sepsis will, in the future, be reduced by optimizing nutritional

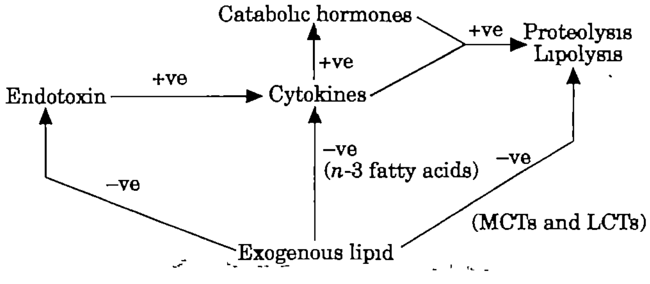

Fig. 3 Interactions of exogenous lipid emulsion and endogenous metabolic alterations in patients with sepsis. Exogenous lipid emulsion particles are similar to very low density lipoprotein particles and can potentially bind endotoxin, thus reducing its effect. The medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) liberate fatty acids, which can be used to provide metabolic fuel. The increased plasma levels of non-esterified fatty acids can inhibit endogenous triacylglycerol lipolysis, thereby preserving not only fat fuel but also lean body mass. The *n*-3 fatty acids in the lipid emulsion may reduce the excessive cytokine response seen in some patients with sepsis

input and manipulation of the immune response, as summarized in *Fig. 3*.

Management of nutrition-induced lipaemia in patients with sepsis

Gross lipaemia occurs in some patients with sepsis receiving parenteral nutrition, although it is rare in those receiving enteral nutrition. It may reflect the supraphysiological rate of entry of lipoprotein particles from the exogenous lipid infusion, in combination with compromised clearance of lipoprotein–TAG from the plasma[68]. The management of such patients has been discussed by Nordenström[227]. Their lipid tolerance should be assessed regularly by inspection of plasma for turbidity and measurement of plasma TAG concentration[228,229]. The lipid infusion rate must be decreased during episodes of hypertriglyceridaemia, although lipid tolerance is likely to change rapidly and should be assessed from time to time as above. More common than hypertriglyceridaemia is the occurrence of hypercholesterolaemia during lipid infusion. This represents the formation of an abnormal lipoprotein particle, lipoprotein X, during intralipid infusion[230,231]. Lipoprotein X is similar to low density lipoprotein but is cleared slowly by the liver[232]. Its formation is favoured by infusion of a 10 per cent lipid emulsion because of the high phospholipid : TAG ratio. Thus, its formation can be reduced by substituting 10 per cent with 20 per cent lipid emulsion[233]. It should also be borne in mind that turbidity in plasma can interfere with some common laboratory tests[234], so close liaison with the clinical biochemistry laboratory is essential.

Summary

Septic shock produced by Gram-negative organisms is a common surgical phenomenon. It can produce profound changes in lipid metabolism, but the mechanisms that induce these changes are poorly understood. Some are brought about by hormones, whereas others are induced by cytokines released in response to endotoxaemia. Optimal nutritional support is essential to meet the metabolic demands of patients with sepsis and lipid emulsions are being used increasingly as a source of this support. Such emulsions not only provide nutrition but are also a powerful means of altering the immunological response of the host.

However, there is still a dearth of knowledge about the mechanisms that lead to lipid abnormalities in patients with sepsis, and about the role of exogenous lipid emulsions as a source of metabolic fuel and regulator of the immunological response. Further research in this area holds the promise of reducing morbidity and mortality rates in such patients.

Acknowledgements

J. S. S. is supported by the Wellcome Trust, to which the authors are grateful for financial support for studies of the regulation of fat metabolism.

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British Journal of Surgery 1996, 83, 1197–1204

Review

Laparoscopic inguinal hernia repair

M. S. L. LIEM and TH. J. M. V. VAN VROONHOVEN

Department of Surgery, University Hospital, PO Box 85 500, 3508 GA Utrecht, The Netherlands
Correspondence to: Dr M. S. L. Liem

Laparoscopic inguinal hernia repair may cause a revolution in general surgery if it proves to be the best treatment for inguinal hernia. Today there are several laparoscopic techniques that have been shown to be feasible. However, no information concerning long-term recurrence rates and cost-effectiveness is available. This review summarizes current knowledge, including all randomized studies that have appeared hitherto, and concludes that it is still premature to advocate a transition from the preferred individualized conventional technique to a laparoscopic technique on a large scale. However, a definite statement on the place of laparoscopic repair may be given in the near future in the light of larger randomized studies.

Considering the growing literature on laparoscopic hernia repair, one might easily be tempted to conclude that it is already an accepted procedure; at this time such a conclusion is premature and based on insufficient research. The quest for the optimal treatment of inguinal hernia was given new vigour after the introduction of minimally invasive surgery. This was enhanced by the media, which stimulated a patient preference for the new minimally invasive technique, and by surgeons' fear of being left behind. Different laparoscopic techniques have emerged, some successful, others not[1,2]. Not all surgeons have supported this new development[3,4] and, more importantly, it has generally been recognized that adequate research should be performed before the world-wide acceptance of this 'controversial' technique[5–8]. Randomized trials were initiated, but so far all reported studies are preliminary, lacking sufficient power; in only one has the newest and conceptually promising totally extraperitoneal technique been used[9–15].

Now, more than 5 years after the introduction of laparoscopic inguinal hernia repair, where do we stand? Are there really significant advantages compared with conventional techniques? If so, which laparoscopic technique should be applied and for what type of hernia? Are we yet confident enough to accept the new technique, or should we wait for the long-term results of the well designed, large, prospective randomized trials that are now in progress?

Methods

This review has employed a database in which all articles included in Medline (Bethesda, Maryland, USA) (on silver platter) concerning inguinal hernia from 1966 to 1994 were stored (search with 'hernia-inguinal/all subheadings'). An update was made in early 1996 with the 1995 edition for 1993–1995. In addition, articles from 14 leading surgical journals published in 1994, 1995 and early 1996 were screened for 'laparoscopic herniorrhaphy'.

Conventional hernia repair

There are numerous conventional techniques used to repair an inguinal hernia[16]. Excellent results (i.e. recurrence rates of less than 2 per cent with follow-up of over 5 years) from specialized hernia centres using their own techniques have been reported[17–20] but, unfortunately, in most of these studies details and appropriate methods concerning follow-up are lacking. Others have recognized these deficits and emphasize the importance of complete and reliable follow-up[20–22]. Moreover, for general surgeons the excellent results reported by specialized centres do not appear to be reproducible in well controlled studies[22–25]. This is confirmed by annual statistics from various countries which always show that 10–15 per cent of inguinal hernia operations are for recurrent hernias[20,26–28]. Another interesting problem is the socioeconomic burden for society of conventional inguinal hernia repair. In the Netherlands, patients with paid employment return to work after an average of 4–6 weeks[29]. Most other countries are no different[30,31]. It would appear that there is room world-wide for improvements in the treatment of inguinal hernia.

Current laparoscopic techniques (*Fig. 1*)

Others have described the history and (early) laparoscopic techniques at length[32–35]. Currently, four techniques, a transabdominal preperitoneal (TAPP) approach, a totally extraperitoneal (TEP) approach, an intraperitoneal onlay mesh (IPOM) technique and simple closure of the internal ring, are still being performed and are discussed here briefly. The first three of these methods are based on the principle of using a mesh prosthesis to cover the defect of the abdominal wall from the inside (*Fig. 1*). The last technique, in which a staple or stitch is used to narrow the internal ring[36], can be used only in small to moderate indirect hernias. It is performed by a few surgeons in a minority of cases (2 per cent) and so any further discussion of this method has been omitted.

A study[37] in the early phase of the development of laparoscopic techniques reported a TAPP technique in 65 per cent of cases and an IPOM repair in 25 per cent. A more recent compilation of over 2500 patients reported a shift in the distribution of these techniques: the TAPP

Paper accepted 3 May 1996

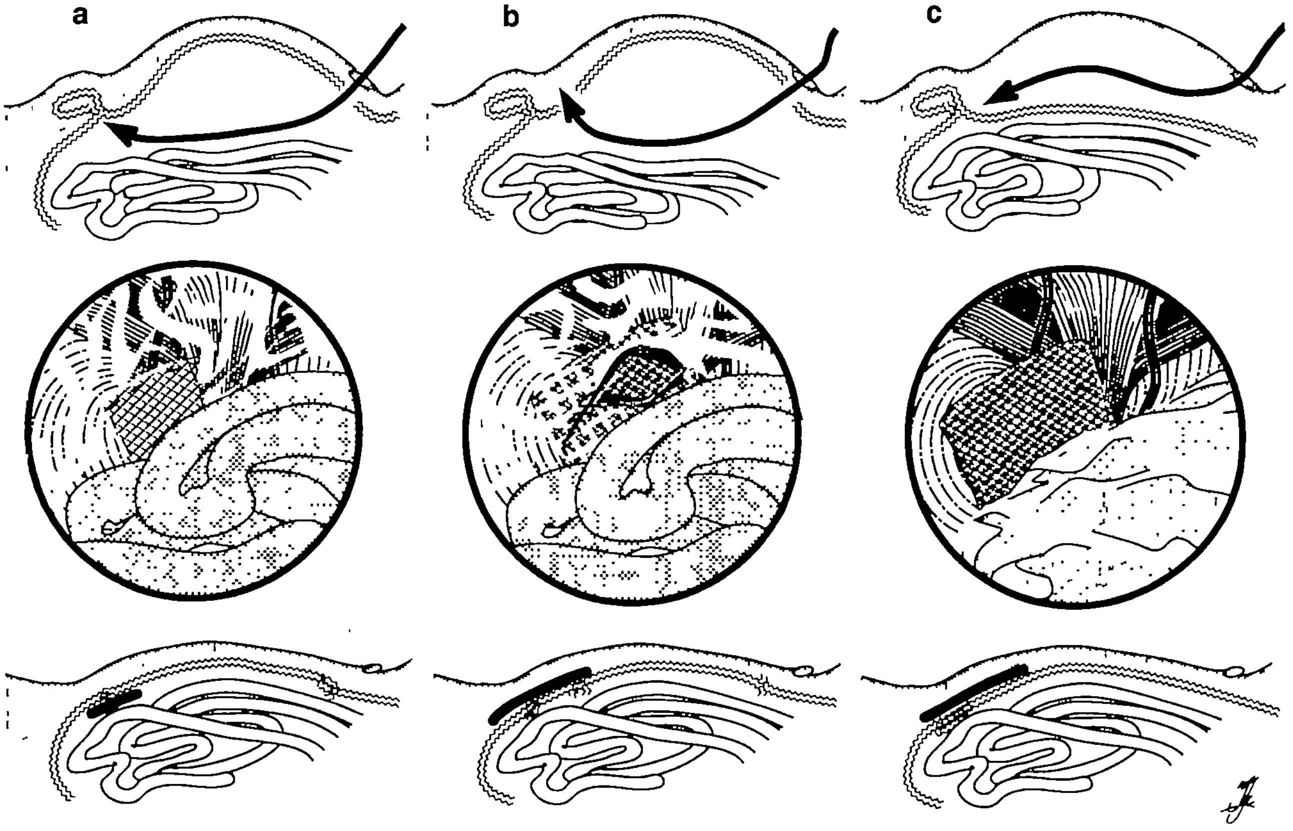

Fig. 1 Current laparoscopic techniques. a Intraperitoneal onlay mesh technique: placement of mesh inside the peritoneum. b Transabdominal preperitoneal technique: preperitoneal placement of mesh through a peritoneal incision. c Totally extraperitoneal technique: preperitoneal placement of mesh without entering the abdomen. Upper panel – approach by pneumoperitoneum (a and b), and by pneumopreperitoneum (c); middle panel – laparoscopic view after mesh placement; lower panel – situation after mesh placement

technique is performed most frequently (60 per cent), followed by the TEP approach (18 per cent) and the IPOM repair (11 per cent)[38]. Thus, there appears to be a preference for mesh placement in the preperitoneal space, in accordance with the ideas of Stoppa[39].

Placement of mesh inside the peritoneum

The IPOM repair can be performed with a low-pressure pneumoperitoneum and so, potentially, under local anaesthesia. The hernia defect is easily recognized and cleared of intestines and adhesions with minimal dissection, making it a relatively easy procedure. The hernia orifice is then covered with intraperitoneally placed polypropylene or expanded polytetrafluoroethylene mesh (size between 7·5 × 7·5 cm and 10 × 15 cm)[13,33,40,41] which is secured with staples, mainly to the peritoneum and to the pubic tubercle and Cooper's ligament. Some of the objections against this method are[32,34]: (1) it cannot be used for medial defects, as the mesh is stapled only medially on to the peritoneum and peritoneum with mesh can still migrate through the hernia orifice into the defect; (2) the structures under the peritoneum cannot be seen accurately, thus when stapling there may be a risk of damage to these structures; and (3) although a laparoscopically placed mesh seems to induce fewer adhesions than mesh placed at laparotomy[42], severe complications (bowel obstruction and fistula formation) have been reported. The conversion rate to a conventional repair varies between 0 and 7 per cent. Mean operating time ranges from less than 20 min to 49 min for unilateral inguinal hernias.

Preperitoneal placement of mesh through a peritoneal incision

After the creation of a pneumoperitoneum, a peritoneal incision is made above the hernia defect to enter the preperitoneal space. Sufficient preperitoneal dissection is necessary to cover the musculopectineal orifice of Fruchaud (the area where all potential hernial defects occur) with a mesh prosthesis. The size of the mesh varies between 7 × 12 cm and 10 × 15 cm. In most cases the mesh is fixed with staples. Afterwards, the peritoneum is closed with either staples or stitches. In a minority of cases it is necessary to convert to an open conventional technique (less than 4 per cent). The TAPP technique is the most reported method, but the majority of authors have not compared it with a standard conventional operation. Additionally, the studies have a short-term follow-up, sometimes only by telephone interview (*Table 1*)[43–49]. Some authors have made a non-randomized comparison with conventional techniques (Bassini and Shouldice) and so-called tension-free techniques[50–53]. Mean operating time varies between 35 and 90 min for unilateral hernias and between 70 and 110 min for bilateral inguinal hernias.

Table 1 Recent studies: transabdominal preperitoneal technique

					TAPP technique						Follow-up	
Reference	Study design	No of patients	Sex ratio (M F)	No. of hernias	Neuralgia	Nerve entrapment	Trocar hernia	Bowel injury	Bowel obstruction	Recurrence	Duration (months)	Details
Panton and Panton[43]	?Retrospective	79	73·6	106	6	0	0	1	0	0	1–12	None
Kavic[44]	Longitudinal	164	138 26	224	3	0	0	0	0	2	5–41	Physical examination at regular intervals
Geis *et al* [45]	Review (?retrospective)	364	269 95	450	3	1	1	0	0	3	6–30	Visits up to 1 year, telephone interview after 1 year
Sandbichler *et al* [46]	Prospective non-randomized	250	231·19	342	18	0	0	0	0	2	2–12	Physical examination at regular intervals
Darzi *et al* [47]	Review (?retrospective)	126	116 10	155	2	0	0	0	1‡	2	Mean 7 (range 1–18)	None
Felix *et al* [48]	Review, prospective series	183	171 12	326	1	0	2	2	1	0	Median 12 (range 6–21)	Physical examination at regular intervals
Winchester *et al* [49]	Non-randomized trial, prospective series	38	36·2	40	3	0	0	0	0	0	Median 26 (range 1–46) weeks	6-week physical examination; telephone interview at 3 and 6 months
Millikan *et al* [50]	Prospective non-randomized comparison	55 *versus* 51, 75 TAPP *versus* 51 open repairs	—	—	0	0	0	0	0	2 *versus* 2	—	—
Brooks[51]	Prospective non-randomized comparison	43 TAPP *versus* 57 open mesh plug	—	116	0	1†	0	0	0	3 *versus* 0	—	—
Wilson *et al* [52]	Prospective non-randomized comparison	121 Lichtenstein *versus* 121 TAPP	—	273	1	0	0	0	0	0 *versus* 0	—	—
Cornell and Kerlikian[53]	Prospective non-randomized comparison	60 TAPP *versus* 27 modified Shouldice	—	—	9	0	0	0	0	1 *versus* 0	Mean 9 (range 2–28)	Physical examination and telephone interview at regular intervals
Total for TAPP technique*		1483			46 (3 1)	2 (0 1)	3 (0 2)	3 (0 2)	2 (0 1)	15 (1 0)		

*Values in parentheses are percentages †This patient required reoperation, a staple was removed which entrapped a nerve ‡This patient died because of aspiration following small bowel obstruction TAPP, transabdominal preperitoneal

Preperitoneal placement of mesh without entering the abdomen

In the newest technique, the TEP approach, the peritoneal cavity is not entered but the preperitoneal space is selectively developed through a subumbilical incision[54–56]. In some studies a dissection balloon is used to facilitate preperitoneal dissection[57], but this can also be done with a Foley catheter[58]. The preperitoneal space is usually maintained with a carbon dioxide pneumopreperitoneum. With the use of an abdominal wall lift this method can be performed without the need for such a pneumopreperitoneum[59]. An endoscopically guided surface repair, which may be less demanding, has also been proposed[60]. After sufficient preperitoneal dissection a mesh prosthesis (size between 8 × 10 cm and 10 × 15 cm) is positioned and, in most cases, fixed with staples; the preperitoneal space is desufflated. The TEP approach is technically more difficult than the others, but it avoids the potential risk of damaging intra-abdominal organs, and it may save time and cost as it is not necessary to incise and close the peritoneum from the inside[2,61]. The conversion rate to another technique, either TAPP or conventional, varies between 4·4 and 8 per cent during the learning curve. Mean operating time is between 42 and 90 min for patients with either unilateral or bilateral inguinal hernias.

Postoperative pain and disability

Hospital stay has been found to be similar for all laparoscopic techniques, most patients being discharged within 24 h. The median hospital stay was between 1 and 3 days. One exception is a German study by Sandbichler *et al.*[46], but their 4 days compare favourably with their 7 days after a conventional repair in the same timeframe. Most of these preliminary studies have focused on technique and complications, but many have also reported minimal use of analgesics, with some patients not requiring postoperative analgesia at all and achieving a successful resumption of daily activities within about 1 week. Unfortunately, both hospital stay and return to normal activity may be associated with surgeon and patient preference; common practice with respect to these issues varies from country to country, which makes comparisons difficult[7]. Some studies have measured postoperative pain. Patients were generally pain-free by 1 week after operation[44,57] and, defining resumption of daily activity by the number of days needed after operation before regaining the ability to drive a car, they returned to normal twice as fast as after a Lichtenstein repair[52]. It is important to note that in none of these studies was a questionnaire to measure activities of daily life or quality of life used.

Complications

Complications may be related to laparoscopy itself, such as lesions caused by needle or trocar insertion (which are quite rare) and events related to pneumoperitoneum (hypercarbia and cardiopulmonary effects)[62–65]. The first does not really apply to the TEP technique, as in this method only the preperitoneal space is opened and developed under vision. However, a pneumopreperitoneum is necessary to maintain the preperitoneal working space and this may result in the development of a rapid and more severe hypercarbia[66,67], although this is not universally acknowledged[68].

Complications related to hernia repair itself include subcutaneous emphysema in the scrotum or lower abdominal wall, scrotal or trocar-site haematoma, seroma, wound infection and neuralgia[38,69]. In most cases neuralgia is a transient complication. Complication rates vary between 8 and 12·4 per cent. Conversion to another technique – in most cases to a conventional approach, but for the TEP procedure it is also possible to convert to a TAPP approach – have been reported for all three laparoscopic operations; conversion is most frequent for the TEP technique[10,13,55].

More severe complications have also been described: meralgia paraesthetica by entrapment, either by fibrous tissue or (in most cases) by a staple placed into the nerve[70–73], and intestinal obstruction due to adherence of small bowel to mesh[74–77]. Naturally, nerve entrapment by staples cannot occur if the mesh is kept in place solely by intra-abdominal pressure, as has been advocated by some authors[29,39,61]. Intestinal obstruction caused by adhesions from bowel to mesh can theoretically not occur if a TEP approach is used, but can be encountered after a transabdominal approach as there is a possibility of mesh contact with bowel if the peritoneum is insufficiently closed. This seems to be confirmed by Phillips *et al.*[38], who collected data on serious complications from 23 surgeons. They reported on 1533 patients who underwent TAPP procedures, complicated in 2 per cent of cases by neuralgia, in 0·3 per cent by bowel obstruction and in two by death (one myocardial infarction and one hepatic failure); 367 patients who underwent TEP procedures had no serious complication.

Recurrences have been reported after all laparoscopic techniques, but are lowest after TEP repair[37,78,79]. Moreover, in a multi-institutional study no recurrences were noted after 578 TEP repairs, but no details about length of follow-up were given[80]. However, during the learning curve there may be a large difference between individuals in terms of recurrence rate, ranging from 0 to 20 per cent during the first 30 cases[61]. Reasons for early recurrences were, in fact, mostly surgical or technical errors. The most common reason was the size of the mesh being too small. It has been suggested that fixation is not necessary if the mesh size is large enough[81,82]. Indeed, not having to provide fixation not only saves time and money, but also obviates another serious complication, namely nerve entrapment by staples. Another frequent reason for a 'recurrence' is not recognizing or insufficiently isolating an indirect hernia because of insufficient anatomical knowledge, too limited dissection or reluctance to convert to another more appropriate technique. This may be encountered especially during the learning curve[80]. Better knowledge regarding the aetiology of early recurrence might lower the incidence of the causative errors.

Comparisons between laparoscopic techniques

Fitzgibbons *et al.*[37] reported on an international non-randomized multi-institutional trial in which the participating surgeons used their preferred technique. There was a 4·5 per cent recurrence rate after a mean follow-up of 23 months. Recurrences were recorded only after TAPP and IPOM repairs; none was noted after TEP repair. However, most TEP procedures were performed by a single surgeon. Recurrence rates for individual surgeons varied from 0 to 14·5 per cent. Although several previous studies had already produced similar results with laparoscopic techniques, the Fitzgibbons study has been suggested as more closely reflecting the value of laparoscopic repair in the population at large, as 21 investigators from both university and private practice settings participated[23].

Felix *et al.*[83] reported a large experience with both the TAPP and TEP techniques, and concluded that the TEP method may be the procedure of choice in most situations. Ramshaw *et al.*[84] concluded from a similar retrospective study that the TEP approach has significant advantages, but a relative contraindication for this technique may be previous lower abdominal surgery.

To enhance comparability there is agreement that hernia defects should be classified accurately in future studies; the Nyhus classification seems to be the most appropriate[85].

Which technique is best suited for which hernia?

Most authors agree on the suitability of laparoscopic repair for bilateral and (multiple) recurrent hernias[1,20,37,85]. No or only one additional port (for the TEP approach) is needed for a bilateral repair and so tissue trauma is less than that during conventional bilateral repair. A recent study of 150 patients having bilateral hernia repair using a TAPP approach reported good results with no recurrence after a median follow-up of 18 months[86]. In (multiple) recurrent hernias after previous conventional repairs the preperitoneal space is usually free from fibrous tissue and adhesions, allowing for an easy and safe dissection with a clear view of all the important structures. It has been suggested that a small indirect hernia can be treated well using an IPOM or TEP procedure, while a complicated recurrent one can be treated better with a TAPP technique. Incarcerated and large scrotal hernias, if they are to be handled laparoscopically at all, may best be dealt with by a TAPP approach[83]. There is so far no agreement about whether laparoscopic repair should be applied to the most common situation: the uncomplicated unilateral inguinal hernia. Nor is there agreement about which technique might best be used. Perhaps a strong patient preference to return to work as quickly as possible may be an exception[14]. All three techniques, but especially the preperitoneal (either TAPP or TEP), may prove useful for different types of hernia.

Evidence from randomized trials

Seven randomized trials have been published in the literature comparing open with laparoscopic hernia repair[9–15]. As all were initiated in 1992 or early 1993, only one has used the TEP technique, which at that time was performed by very few surgeons. All trials focused on short-term outcome measures with a short follow-up, so meaningful statements concerning recurrence rates are not available. All seven reports confirmed the observation of previous non-randomized studies to a greater or lesser extent: less postoperative pain, less use of analgesics and (in four trials) faster recovery after a laparoscopic repair than after an open operation. In the remaining three studies recovery was slightly better for patients in the laparoscopic group than for those having open repair, but this was not statistically significant (*Table 2*)[87].

Lawrence *et al.*[15] state that thousands rather than hundreds of patients should be included in randomized trials to detect differences in recurrence rates between laparoscopic and open repair. It is this outcome that has generally been considered the most important measure in the evaluation of hernia surgery[88]. For patients themselves it also seems to be the most relevant issue: 74 per cent of those in one study considered long-term recurrence the most important outcome measure, not the speed of recovery[15].

In two randomized studies quality of life was measured[14,15]. There is increasing interest in this outcome measure and it is now incorporated more frequently in surgical randomized trials[89]. Quality of life was measured with the Short-Form 36 questionnaire in one study and did not show differences for most dimensions, except pain, energy and social function. Interestingly, no difference for the dimension 'physical mobility at 10 days' was noted[15]. Another questionnaire, the Nottingham Health Profile, was applied by Barkun *et al.*[14], but the results of this were compared only with baseline and not with the conventional repair technique. Nevertheless, a greater improvement in quality of life has been noted by them after laparoscopic than after open repair. Several authors[7,10] have advocated the use of a more objective outcome measure, such as a physical performance test, to measure postoperative recovery, as return to work may vary with a patient's motivation, disability cover and external uncontrolled advice. Even in randomized trials there may be a bias if surgeons, family physicians and nurses tend to give different advice to patients after conventional repair than after laparoscopic repair[14].

Studies of cost are becoming increasingly important but, regrettably, in the field of minimally invasive surgery they have lacked scientific objectivity and are often based on data that are suspect[90]. In a true cost–effectiveness analysis within randomized trials, all relevant costs from a societal point of view and not just hospital charges[91,92] should be calculated and compared[93]. In two randomized trials, as in the preliminary studies reviewed here, materials were costed but other relevant costs, for instance cost of an additional day of sick leave[94], were not. Two trials performed a cost analysis, but not a true cost–effectiveness analysis[95].

Recommendations and the future

Most surgeons prefer the placement of a large mesh prosthesis in the preperitoneal space, by either a transabdominal or an extraperitoneal approach. The TEP technique is very promising, but its major drawback may be difficulty mastering it. The most popular method is the TAPP technique, which may also be easier to learn. While acceptable results can be achieved with this technique, there is a potential, although quite rare, for severe

Table 2 Randomized trials comparing open with laparoscopic hernia repair

Reference	Year	Technique	No. of patients	Power calculation	Main endpoint(s)	Postoperative pain	Costs	Return to activity (days)	Follow-up (months)	Recurrence (open *versus* laparoscopic)
Stoker *et al*[9]	1994	Moloney darn[87] *versus* TAPP	75 *versus* 75	Yes, 50 per cent reduction in analgesics	Postoperative pain, return to activity and work	Visual Analogue Scale (mean 3 1 *versus* 1 8)	Extra materials £168	28 *versus* 14 (median)	7 (mean)	0 *versus* 0
Payne *et al*[10]	1994	Lichenstein *versus* TAPP	52 *versus* 48	No	Operating time, complications, recuperation, recurrence rate, costs	Not measured, but exercise test performed	Extra supplies $426, and hospital charges (mean $2494 *versus* $3093)	17 *versus* 8·9 (mean)	10 (median)	0 *versus* 0
Champault *et al*[11]	1994	Shouldice *versus* TEP	89 *versus* 92	No	Mortality, morbidity, operating time, hospital stay	Visual Analogue Scale (significantly different)	Not calculated	24 3 *versus* 12 5 (mean)	12 (mean)	0 *versus* 0
Maddern *et al*[12]	1994	Darn *versus* TAPP	44 *versus* 42	No	Pain score, activity levels, analgesia requirements, return to work	Analogue Scale (not significantly different)	Not calculated	Not significantly different	8 (median)	0 *versus* 2
Vogt *et al*[13]	1995	Traditional repair (Bassini, McVay) *versus* modified onlay mesh	31 *versus* 30	No	Not described in methods	Not measured; reduction in minimal narcotic requirements	Not calculated	18 5 *versus* 7 5 (mean)	8 (mean)	2 *versus* 1
Barkun *et al*[14]	1995	Preference of surgeons *versus* TAPP	49 *versus* 43	Yes, but not specified	Patient convalescence	McGill Pain Questionnaire not significant	Direct costs Can $1224 *versus* $1718	10·9 *versus* 9 6 (median)	14 (median)	1 *versus* 0
Lawrence *et al*[15]	1995	Modified two-layer Moloney darn *versus* TAPP	66 *versus* 58	Yes, one-sided	Short-term complications	Linear Pain Score significant on moving and coughing	Theatre costs £268 *versus* £850	28 *versus* 22 (median)	—	0 *versus* 1
Total			406 *versus* 388							3 *versus* 4

TAPP, transabdominal preperitoneal laparoscopic repair; TEP, totally extraperitoneal laparoscopic repair complications such as bowel injury and obstruction. Even the small risk for such complications may not be acceptable for either patient or surgeon. Nevertheless, the TAPP approach might prove useful for its own set of indications and may be used in a complementary fashion to other methods.

Hitherto, randomized trials were small and designed to look at short-term outcome measures; they have not been able to detect differences in recurrence rates between operations. These studies were unequivocal about the advantage of laparoscopic herniorrhaphy over open repair in terms of faster rehabilitation. However, the most important question cannot yet be answered: are long-term recurrence rates for laparoscopic repairs better or worse than those for open repairs? Currently, there are four large trials (in order of initiation in Sweden, the Netherlands, UK and France) which have included or intend to include over 1000 patients each and these may eventually yield a definitive answer[96]. Some of these trials use the TEP approach for comparison and are conducting a cost-effectiveness analysis. As these studies are multicentred they may also prove more attractive in terms of general validity. Every general surgeon should be capable of performing laparoscopic inguinal hernia repair with acceptable rates of complications and recurrence. If not, we should question the world-wide introduction of this new technique.

We believe it is not yet appropriate to convert from a preferred individualized approach to a laparoscopic technique on a large scale. If such a conversion seems warranted in the future, the problems of the learning curve should not be regarded lightly if unacceptable rates of technical error and early recurrence are to be avoided. If necessary, training centres may be established to allow a controlled transition from conventional to laparoscopic hernia repair.

Acknowledgements

The authors thank Dr A. Gerritsen van der Hoop, Department of Surgery, University Hospital, Utrecht, and Dr Y. van der Graaf, Department of Clinical Epidemiology, University Hospital, Utrecht, for critically reviewing the manuscript and for helpful comments.

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British Journal of Surgery 1996, 83, 1205–1210

Division of the sphincter of Oddi for treatment of dysfunction associated with recurrent pancreatitis

J. TOOULI, V. DI FRANCESCO, G. SACCONE, J. KOLLIAS, A. SCHLOITHE and N. SHANKS

Gastrointestinal Surgical Unit, Department of Surgery, Flinders Medical Centre, Bedford Park, Adelaide, 5042 South Australia, Australia
Correspondence to: Professor J. Toouli

Increasing evidence suggests that motility disorders of the sphincter of Oddi may lead to episodes of recurrent pancreatitis in a small proportion of patients with the diagnosis of idiopathic recurrent pancreatitis. Over 10 years, 35 patients have been identified and treated for this condition. The aim of the study was to assess symptomatic outcome in these patients. Following the exclusion of common causes of pancreatitis the patients underwent sphincter of Oddi manometry. Patients with manometric abnormalities and three with normal manometric findings underwent treatment. Twenty-six patients with persistent symptoms underwent total division of the sphincter via open sphincteroplasty and septectomy. Patients were followed up according to symptoms and classed as having a cure, mild symptoms or no change. At a median follow-up of 24 (range 9–105) months, 15 of the 26 patients were cured, eight had only mild symptoms and three remained unchanged. In the majority of patients with a good clinical outcome, manometry had demonstrated sphincter of Oddi stenosis. Total division of the sphincter of Oddi is associated with good symptomatic outcome in patients with recurrent episodes of pancreatitis and documented sphincter of Oddi stenosis.

The cause of acute pancreatitis in the majority of patients is usually obvious; for most Western countries the major causes are alcohol consumption or gallstones[1,2]. However, in a significant number of patients the cause is unknown and when the episodes of pancreatitis recur a diagnosis is made of idiopathic recurrent pancreatitis[1–6]. The authors have previously described sphincter of Oddi motility disorders in a group of patients who presented with the clinical diagnosis of idiopathic recurrent pancreatitis, and postulated that sphincter of Oddi dysfunction may be one of the causes of this condition[5]. Sphincter of Oddi dysfunction has also been shown to be associated with recurrent biliary-type pain in some patients following cholecystectomy[7], and in those with a significant motility disturbance such as manometric stenosis, division of the sphincter was associated with relief of symptoms[8]. Other reports have also proposed an association between sphincter of Oddi abnormalities and the development of pancreatitis[9], and division of both the biliary and pancreatic sphincter of Oddi has been proposed as treatment for this condition[10]. The major difficulty in treating these patients has been the selection of patients who will best benefit from sphincter division.

Over 10 years ago the authors embarked on a prospective protocol which aimed to treat patients presenting with recurrent pancreatitis of unknown aetiology based on sphincter of Oddi manometric findings. The results of this policy have been recently reviewed and are presented in this report.

Patients and methods

Between January 1984 and December 1994, 35 consecutive patients with the clinical diagnosis of idiopathic recurrent pancreatitis were evaluated and treated. All patients had other causes of pancreatitis excluded by relevant investigations, done mainly by the referring physicians and reviewed by the authors. All patients had at least two documented episodes of pancreatitis with abnormally raised serum amylase values, and most had several documented episodes requiring inpatient hospital treatment.

Investigations

During the initial interview a detailed history was obtained and recorded on a standardized form designed to allow subsequent analysis of symptoms. Any provocative factors (such as specific foods, medications or alcohol) for initiating episodes of pancreatitis were identified and this information was used for subsequent treatment of the patient.

All patients underwent endoscopic retrograde cholangiopancreatography (ERCP) to eliminate a structural cause for the pancreatitis. In one patient with an intact gallbladder, bile was aspirated through the ERCP catheter and examined for the presence of microcrystals of cholesterol.

Management

Initially, patients were treated conservatively, aiming to avoid any identifiable provocative factors and to abstain totally from alcohol consumption. This did not prove difficult as in this series of patients the selection process excluded those with clinical evidence of alcohol dependence. Patients were followed clinically, initially at monthly intervals for 3 months and subsequently every 3 months. If symptoms improved or were tolerated, no further treatment was given. However, in the majority of patients the episodes of pancreatitis continued. These patients were next investigated by sphincter of Oddi manometry and a morphine–neostigmine provocation test.

Patients with a provisional diagnosis of sphincter of Oddi dysfunction were treated by division of the sphincter. Initially the division was confined to the biliary sphincter and performed endoscopically or by open operation. However, as time progressed and data from other studies in the authors' unit became available, it was decided that both the biliary and pancreatic components of the sphincter of Oddi should be divided by open transduodenal sphincteroplasty and septoplasty.

Manometry

The technique for sphincter of Oddi manometry has been described previously[7]. In brief, a triple-lumen manometry catheter was positioned across the sphincter of Oddi after its

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Paper accepted 24 April 1996

introduction through the biopsy channel of a standard duodenoscope In patients in whom endoscopic sphincter of Oddi manometry was not possible, intraoperative recordings were attempted. Normal pressure values for the sphincter have been defined in previous studies[11]. Sphincter of Oddi dysfunction has been arbitrarily subdivided into two major categories of stenosis or dyskinesia based on the manometric findings. Sphincter of Oddi stenosis was diagnosed in patients with an abnormally raised basal pressure in excess of 40 mmHg. Sphincter of Oddi dyskinesia consisted of one or more motility disorders, such as paradoxical response to cholecystokinin-octapeptide administration, rapid contraction frequency or excess retrograde contractions[12].

Provocation test

The morphine–neostigmine provocation test has also been described previously[13]. A positive test was recorded when the pain was reproduced, as recorded by a linear analogue scale, by the administration of the drugs and there was an associated rise above the upper limit of normal in serum levels of amylase and liver transaminases

Sphincter division

Endoscopic sphincterotomy was performed by means of standard techniques The biliary sphincter was divided by a mixture of coagulation and cutting current with a Demling-type sphincterotome[14]

Sphincteroplasty and septectomy were performed under general anaesthesia and through a right subcostal transverse abdominal incision. The common bile duct was identified after division of adhesions usually present between the duodenum and gallbladder bed. A choledochotomy was performed and a 'step catheter' was passed down the bile duct and into the duodenum (*Fig. 1a*). The tip of the catheter could be palpated through the duodenal wall, thus facilitating placement of the duodenotomy. A small duodenotomy was made and the end of the step catheter grasped to bring the papilla into ready access. A routine sphincteroplasty was made of at least 2 cm in length so that the whole length of the biliary sphincter was divided (*Fig. 1b*) Mucosa-to-mucosa fine cat gut sutures were used for haemostasis and mucosal apposition. On completion of the biliary sphincteroplasty, the step catheter was elevated upwards to expose the opening of the pancreatic duct (*Fig 1c*) The manometry catheter was then inserted into the pancreatic duct to record from the pancreatic sphincter. In four patients the pancreatic sphincter was stenosed to such a degree at the time of the open operation that manometry was not possible. Cannulation could be achieved only by careful insertion of the finest of lacrimal probes. Under these circumstances it was considered justifiable to make the diagnosis of stenosis in these four patients. Once the pancreatic duct had been cannulated, the pancreatic sphincter was divided for a length that allowed free passage into the pancreatic duct (*Fig. 1d*). Often a gush of pancreatic juice escaped from the duct as the stenosed sphincter was finally divided. The septoplasty completed, the duodenum was then closed transversely

Follow-up

All patients were followed initially at monthly intervals for 3 months, then 3-monthly for 1 year, and subsequently yearly. Most patients were reviewed clinically by one of the authors; however, a number of patients had travelled from other Australian states for treatment and, after the initial follow-up, were reviewed by the referring doctor. The patients' records were then independently reviewed by two of the co-authors (V. di F. and J.K.). The patients were contacted by postal questionnaire and by telephone, and the results of treatment scored according to the following simple scale: 0, no symptoms; +, mild symptoms that are readily controlled by occasional analgesics and do not require medical or hospital treatment; NC, no change or worse.

Statistical analysis

Data were stored on a personal computer and analysed for presentation. Values are presented as median (range). Review of the patients' case notes was approved by the Flinders Medical Centre Clinical Investigations Committee.

Results

Patients

Most (30) patients were women and the median age was 39·5 (range 20–70) years. No patient had a history of heavy alcohol intake and only seven consumed any alcohol, reported at between one and seven regular drinks per week. There was no significant history of drug intake and ten smoked cigarettes. Six patients were nurses by profession; there was no evidence of analgesia abuse in this subgroup.

Previous medical history was non-contributory and all but one patient had had cholecystectomy prior to referral. It was difficult to determine the onset of pancreatitis in relation to the cholecystectomy in all patients. In at least eight patients documented pancreatitis had preceded cholecystectomy. In 20 patients cholecystectomy had been performed for stones, and the other 15 had had the operation in an effort to treat the pancreatitis. Eight patients had undergone endoscopic sphincterotomy at the time of referral. The sphincterotomy had not altered the episodes of pancreatitis.

Presenting symptoms

The most consistent symptom, which was reported by all patients, was recurrent pain. Patients were able to distinguish between recurrent major episodes of pain and more frequent minor episodes. The major episodes occurred at a median frequency of one per month (range of one every 2 days to one per year).

In half the patients the pain started in the epigastric region and radiated to either the back or right upper quadrant of the abdomen. In seven patients the pain originated in the right upper quadrant and radiated to the back, whereas in ten it started and did not radiate from the right upper quadrant. The pain was described as sharp and constant by 31 patients, with two describing it as cramping and two as burning.

Thirty-one patients experienced nausea in association with the pain and 19 had associated vomiting. The episodes of pain were related to food intake by seven patients and were reported to be aggravated by alcoholic drinks in seven and by taking codeine in nine. There was no significant temporal relationship to the onset of symptoms.

All the patients had required hospital admission for treatment of pancreatitis on at least one occasion, but most had had numerous admissions. The episodes of pancreatitis were usually mild, with pain lasting between 3 and 96 h. In the majority, pain was relieved by parenteral analgesics but in seven analgesics had no effect. Only two patients experienced severe pancreatitis with abnormal prognostic factors. The pancreatitis resolved with conservative treatment.

Investigations

All patients demonstrated abnormally raised serum amylase levels on at least two presentations with

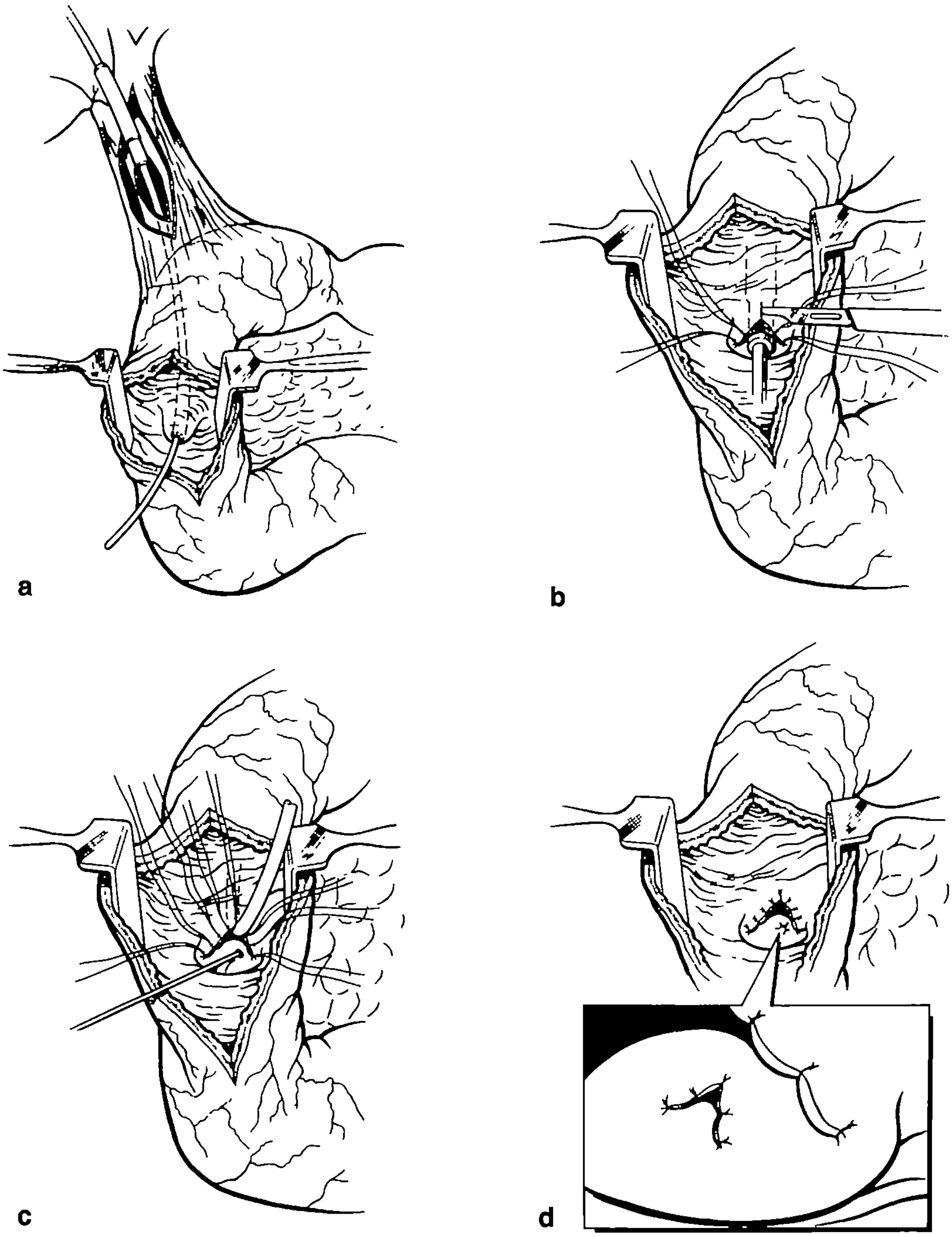

Fig. 1 Sphincteroplasty and septectomy. **a** A step catheter is introduced via a choledochotomy through the sphincter of Oddi and into the duodenum, thus facilitating identification of the papilla for precise positioning of the duodenotomy. **b** Biliary sphincteroplasty is performed and the edge is sutured together for mucosa-to-mucosa apposition. **c** The step catheter is elevated upwards to identify the pancreatic duct opening. A small catheter is then inserted into the pancreatic duct. **d** At completion of the operation on the sphincter, both the biliary and pancreatic parts have been divided completely

abdominal pain. In 25 pancreatitis was accompanied by abnormally raised levels of liver transaminases.

ERCP was attempted in 33 patients and was unsuccessful in two because of tight stenosis. In four of the 31 successful ERCPs the pancreatic duct was not adequately visualized. In the other 27 patients a good diagnostic pancreatogram was obtained. Initial ERCP had demonstrated slight ductal irregularities in only six patients. In a further four the bile duct was mildly dilated but in the remaining patients no abnormalities were observed. Overall, 14 of the 35 patients experienced abdominal pain during ERCP. One patient who had originally declined treatment by division of the sphincter was treated conservatively for 10 years. In this patient the initial ERCP showed no abnormalities. However, a repeat ERCP performed at the time of reassessment 10 years later demonstrated pancreatic duct changes consistent with chronic pancreatitis. Furthermore a number of calculi were present in a dilated pancreatic duct. There were no patients with pancreas divisum anomaly, as such cases had been excluded from this study.

Morphine–neostigmine test

This provocation test was performed in 17 patients and the results were abnormal in ten. All those with an abnormal test result exhibited abnormal manometric recordings. In addition, six of the other seven patients also displayed abnormal manometric findings, which may reflect the mechanism of selection of the patients for this series.

Manometry

Either endoscopic or intraoperative manometry was performed in 33 patients. Stenosis of the sphincter was recorded in 24 patients. In four of these patients the diagnosis of stenosis was made without the aid of manometry as the sphincter was too tight to allow insertion of the recording catheter. In these four patients an attempt to record sphincter pressures was made at open surgery. An inability to insert the manometry catheter through a tight sphincter at open operation was taken as consistent with the diagnosis of stenosis. In six patients manometry demonstrated dyskinesia and in the other three the manometric findings were normal.

Treatment

The initial form of therapy for this group of patients varied (*Fig. 2*), reflecting the changes in our understanding of this disorder. In seven patients prolonged medical treatment with antispasmotic drugs such as hyoscine was the initial treatment. In a further seven endoscopic sphincterotomy was performed. In two patients operative sphincteroplasty was carried out and in 19 the initial treatment was operative sphincteroplasty and septoplasty. A further seven underwent operative sphincteroplasty and septoplasty after failure of the initial therapy, resulting in 26 patients who had this procedure.

The operation was not associated with any significant complications. In particular there was no evidence of significant pancreatitis in any patient in the postoperative period, and no operative mortality. Two patients had mild hyperamylasaemia after operation, but this did not prolong their recovery.

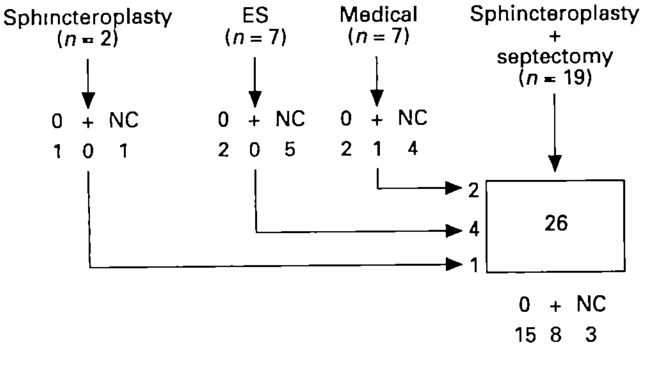

Fig. 2 Results of treatment for all 35 patients ES, endoscopic sphincterotomy; 0, cure; +, mild symptoms; NC, no change

Follow-up

The symptomatic follow-up of all patients is summarized in *Fig. 2*. In patients who did not initially have sphincteroplasty and septoplasty, the outcome was poor. In four of the seven patients having conservative therapy, there was no change in symptoms at a median of 24 (range 8–48) months of follow-up. Two of these patients were subsequently treated by sphincteroplasty and septoplasty. Five of the seven patients who had endoscopic sphincterotomy initially experienced no change in symptoms at a median of 12 (range 3–46) months after operation, and four of these subsequently underwent sphincteroplasty and septoplasty. Similarly, one of the two patients who had had operative sphincterotomy showed no improvement in symptoms at 23 months and then had a septoplasty.

The relationship between manometric diagnosis and initial medical therapy or biliary sphincterotomy is shown in *Table 1*. Sphincter of Oddi stenosis was associated with a poor outcome after medical therapy and for therapy directed only at the biliary component of the sphincter.

Sphincteroplasty and septoplasty were performed in 26 patients with median follow-up of 24 (range 9–105) months; 15 reported no further symptoms and eight had only mild symptoms that were treated by mild oral analgesics. None of these patients has required hospital treatment for pancreatitis. Therefore, 23 of the 26 patients who had sphincteroplasty and septectomy experienced clinically significant improvement from this procedure and none required subsequent medical treatment for recurrent pain. In three patients the operation did not alter the frequency or severity of symptoms (*Table 1*). Division of both the biliary and pancreatic sphincter is associated with a good outcome following the diagnosis of sphincter stenosis (*Table 1*).

Table 1 Sphincter of Oddi manometric diagnosis and therapy

	Manometric findings			
Symptoms	Normal	Stenosis	Dyskinesia	Total
Conservative				
0	0	0	2	2
+	0	1	0	1
NC	1	3	0	4
Endoscopic sphincterotomy				
0	0	1	0	1
+	0	0	1	1
NC	1	4	0	5
Operative sphincteroplasty and septectomy				
0	1	14	0	15
+	0	6	2	8
NC	0	3	0	3

0, No symptoms, +, mild symptoms; NC, no change

Discussion

In this selected series of patients presenting with an initial diagnosis of idiopathic recurrent pancreatitis, sphincter of Oddi dysfunction was identified and total division of the sphincter led to a high probability of cure. A subjective assessment of outcome was made and thus a simple three-scale scoring system that did not require detailed recall was used. Grades of improvement or worsening of symptoms were not evaluated as these symptoms could not be assessed accurately. This series of patients was evaluated prospectively over the course of 10 years using a protocol that changed as accumulated data from other parallel studies pointed to the clinically most relevant form of therapy. The fact that it has taken 10 years to accumulate a series of only 35 patients reflects the relative rarity of this condition. It would be irrelevant to relate this value either to numbers of patients with pancreatitis treated in the same period or to those with dysfunction of the biliary sphincter of Oddi because most of the patients were tertiary referrals, often from a long distance from this institution, reflecting the authors' interest in this condition.

The presenting symptoms and signs were similar to those in previous series reported both by the authors[5] and by other investigators[6]. The clinical presentation is that of pancreatitis associated with no obvious cause. All except one of the present patients had had cholecystectomy performed previously in an attempt to remove the cause of recurrent pancreatitis; hence the question of passing cholesterol crystals from sludge in the gallbladder was not of relevance. In the one patient with an intact biliary tract the bile was examined for crystals, but these were not found. The association between passage of cholesterol crystals and pancreatitis has been well demonstrated in previous studies[15,16]. It might be postulated that the passage of crystals or microcalculi may have produced changes in the sphincter that are responsible for the recurrent episodes of pancreatitis, although there is no evidence to support this contention.

An interesting association with this disorder is the susceptibility of some patients to opiates and the induction of pancreatitis following their administration. This association was not universal for all patients, so that the morphine–neostigmine test has not proven to be a reliable investigation in selecting patients for treatment[13]. In this series of patients there was a higher association between the morphine–neostigmine test, manometric findings and outcome than has been found in other series[9]. However, this may reflect the highly selected nature of this group of patients and the mechanism by which they were screened and offered treatment. For most patients, inclusion in the series required that the majority of screening investigations be positive. A previous study of an unselected group of patients demonstrated that, although the morphine–neostigmine test was a useful screening investigation, it could not be used to select patients for treatment[13].

In a previous series of patients an association was demonstrated between sphincter of Oddi manometric abnormalities and idiopathic recurrent pancreatitis[5]. In particular, sphincter of Oddi stenosis as characterized by an abnormally raised basal pressure was noted[5]. This finding has been reaffirmed in the present series of patients, although the nature of their selection does not permit us to draw conclusions regarding the relative frequency of sphincter stenosis in patients with idiopathic recurrent pancreatitis. The cause of the stenosis is unknown. Histological examination was not performed routinely in these patients because of the difficulty of obtaining an adequate specimen safely; however, based on palpation and appearance at operation, the papilla was judged fibrotic rather than hypertrophic. Approximately one-third of the patients had previously undergone either endoscopic or operative biliary sphincterotomy, so it is possible that this procedure may have resulted in stenosis of the pancreatic sphincter. However, in most of these patients the pancreatitis had predated sphincterotomy, suggesting that, if it were a contributory factor, it would be the cause in only a small number of patients. Studies have shown that separate recording from the pancreatic sphincter in patients with recurrent pancreatitis will demonstrate manometric stenosis in the absence of stenosis of the biliary sphincter[17,18].

The aetiology of sphincter of Oddi dysfunction is unknown. One potential cause is the continual and intermittent passage of gallstones through the sphincter, which may cause trauma resulting in inflammatory changes and fibrotic repair. However, this cannot have been the cause in all of the present patients as 15 did not have gallstones. Possibly this condition may reflect a spontaneous motility disorder of the sphincter similar to other such disorders of the gastrointestinal tract. Like other motility disorders and biliary sphincter of Oddi dysfunction, it is more common in women. However, an association or causal relationship with female reproductive hormones has not been demonstrated.

Treatment of sphincter of Oddi dysfunction which involves only the biliary sphincter is by endoscopic sphincterotomy. In a prospective series of patients it was demonstrated that endoscopic division of the sphincter in those with manometrically demonstrated stenosis resulted in a high rate of cure[8]. In a previous series[10] it had also been demonstrated that the operation of sphincteroplasty and pancreatic duct septoplasty was associated with pain relief in a subgroup of patients who presented with recurrent pancreatitis or pancreatic pain. However, in both these earlier series the patient population was heterogeneous and included some with an alcohol aetiology for the pancreatitis and others who were dependent on narcotics. Hence, although the outcome was good for a majority of patients, it was not clear how they could be effectively selected for operation.

The results of the present series demonstrate the value of sphincter of Oddi manometry for the selection of patients to undergo total division of the sphincter by sphincteroplasty and septectomy. An observable manometric stenosis is associated with a high rate of cure from recurrent pancreatitis following sphincter division. In this series the sphincter was divided by open operation and the authors were not tempted to explore the possibility of endoscopic pancreatic sphincter division. Sporadic reports have appeared recently of this procedure[6,8,19–21]. It is crucial, whichever approach is used, that the pancreatic duct be left wide open at the end of the procedure as oedema at the site of the operation may produce duct obstruction and the possibility of a further episode of pancreatitis in the post-procedure period.

Sphincter of Oddi dysfunction as a cause of idiopathic recurrent pancreatitis is an uncommon but debilitating condition. When suspected, the diagnosis is readily made by endoscopic sphincter of Oddi manometry. If a stenosis is recorded, division of both the pancreatic and the biliary sphincter has been shown to be associated with good results on long-term follow-up.

Acknowledgements

The secretarial assistance of Amanda Sowter in the preparation of this manuscript is acknowledged.

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British Journal of Surgery 1996, 83, 1211

Case report

Pancreatitis in childhood associated with villous adenoma of the ampulla of Vater

M. ARIF MATEEN KHAN,
D. M. THOMAS* and E. R. HOWARD
*Departments of Paediatric Surgery and *Histopathology, King's College Hospital, Denmark Hill, London SE5 9RS, UK*
Correspondence to: Professor E. R. Howard

Pancreatitis in childhood is rare[1] and, unlike most adult disease, is usually attributable to a specific lesion. A unique association of relapsing pancreatitis with an adenoma of the ampulla of Vater is reported.

Case report

A 14-year-old boy presented with a 10-year history of recurrent central abdominal pain. Two estimations of serum amylase were found to be increased. Endoscopic retrograde cholangiopancreatography revealed a dilated pancreatic duct with obstruction in the region of the head of the pancreas. In view of the recurrent nature of the symptoms and the obstruction of the pancreatic duct, pancreatoduodenectomy was undertaken. There were no postoperative complications, and no further attacks of pancreatitis have occurred since operation.

On macroscopic examination of the specimen, the ampulla was mildly enlarged and firm and its covering mucosa appeared normal. The pancreas was firm; the ducts appeared slightly dilated and contained mucinous plugs. Microscopy showed an exophytic, tubulovillous adenoma within the ampulla, 5 mm in diameter with mild epithelial dysplasia. Chronic inflammation was present throughout the pancreas (*Fig. 1*).

Discussion

Pancreatic duct obstruction in association with pancreatitis in children has been described with helminthic infestation, gastric duplication cysts and anomalous drainage of the pancreatic duct into the fourth part of the duodenum, common pancreatico–biliary channels and annular pancreas[1]. Because of the rarity of these conditions, diagnosis is often delayed as it was in the present report. Dabadie *et al.*[2] reported a case of acute pancreatitis caused by the impaction of a paper clip in the ampulla of a 14-month-old child. A large papillomatous tumour with a weight of 750 g has been described arising within the bile duct of a 4-year-old child, but this tumour was not associated with pancreatitis[3].

In adults adenomas are the commonest benign tumours of the extrahepatic biliary tree, and approximately half are situated near the ampulla of Vater. Patients commonly present with right upper quadrant pain and jaundice. These tumours may contain areas of dysplasia and carcinoma, and these features have been reported previously in three patients[4]. Furthermore, a recent study from Japan demonstrated carcinoembryonic antigen and carbohydrate antigen 19-9 in ampullary adenomas with mild-to-moderate dysplasia, an appearance which is also seen in colorectal carcinoma[5]. Surgical management therefore includes complete excision to ensure against later malignant transformation, as in the present case.

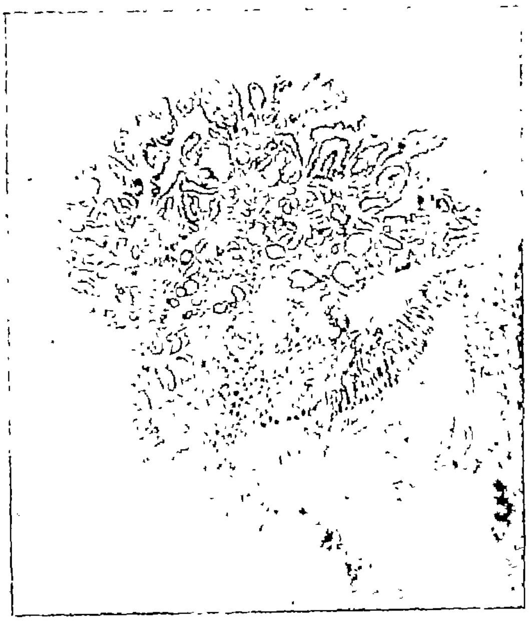

Fig. 1 Histological section of a tubulovillous adenoma, 5 mm in diameter, arising within the ampulla of Vater. The epithelium was mildly dysplastic

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Paper accepted 23 November 1995

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British Journal of Surgery 1996, 83, 1212–1214

Technique of laparoscopic splenectomy with a powered vascular linear stapler

W. F. A. MILES, J. D. GREIG, R. G. WILSON and S. J. NIXON

Department of Surgery, Western General Hospital, Edinburgh, UK
Correspondence to: Mr W. F. A. Miles, Department of General Surgery and Coloproctology, St James Wing, St George's Hospital, Blackshaw Road, London SW17 0QT, UK

The spleen may be removed by a laparoscopic technique, although the benefits and associated morbidity of this approach are unknown. This study reports a series of 28 consecutive patients (15 women; median age 39 (range 17–84) years) considered for laparoscopic splenectomy, because of idiopathic thrombocytopenia in 14, human immunodeficiency virus-related thrombocytopenia in seven, autoimmune haemolytic anaemia in four, lymphoma in two and chronic lymphocytic leukaemia in one. In 23 cases dissection was completed laparoscopically, with the patient in the right lateral position, using a four-cannula technique. Vascular isolation was achieved with an Endo-GIA (powered vascular linear stapler). The spleen was removed by morselation within a retrieval bag (18 patients) or via either a Pfannenstiel or subcostal incision (five). The last 14 procedures have all been completed successfully in a mean operating time of 105 min with discharge from hospital within a median of 3 days. One patient developed a clinically apparent deep venous thrombosis 23 days after operation, for which he required readmission. Elective laparoscopic splenectomy is a feasible although technically demanding operation which may be performed safely and without associated mortality by surgeons experienced in laparoscopic techniques.

The significant benefits of laparoscopic surgery may not be realized by intra-abdominal operations that require prolonged and difficult dissection or gastrointestinal anastomosis[1–3]. Although the spleen is a relatively inaccessible organ with a large and fragile blood supply, its peritoneal attachments are easily defined and, once mobilized, it has a single vascular pedicle. This makes the spleen a suitable organ for laparoscopic surgery[4–10] from which a rapid recovery might be expected. The three major obstacles to laparoscopic splenectomy are: access, vascular isolation and retrieval of the organ. Each of these has been overcome by the technique described below.

Patients and methods

In a 40-month period, from February 1992, 28 patients (15 women) of median age 39 (range 17–84) years were referred for splenectomy. Fourteen patients had idiopathic thrombocytopenia, seven had thrombocytopenia related to human immunodeficiency virus (HIV) infection, four had autoimmune haemolytic anaemia, two had malignant lymphoma and one had chronic lymphocytic leukaemia. Laparoscopy was performed in all patients except two where there was massive splenomegaly that would have precluded retrieval of the dissected spleen

Operative technique

Preparation All patients with HIV-related thrombocytopenia received platelet transfusions before surgery. Those with autoimmune haemolytic anaemia and idiopathic thrombocytopenia were given platelet transfusions following division of the splenic hilum. All patients received Pneumovax (Pasteur Merieux, Maidenhead, UK) before operation and prophylactic antibiotics were given during the operative period.

Technique. The patient is placed with the trunk rotated towards the right lateral position (*Fig. 1a*), slightly head up and with a 10° break in the table. Excessive forward rotation, which causes the spleen to fall forwards, can impair access particularly with larger spleens and so is avoided. The surgeon and assistant (camera operator) stand to the right of the patient. A 1-cm supraumbilical incision is made and carbon dioxide insufflation is performed through a Veress needle to an inflation pressure of 14 mmHg. A 10-mm disposable cannula is inserted and laparoscopy is performed with a 0° telescope. The anterior and posterior adhesions to the spleen are assessed, and then three 5-mm cannulas are inserted in the epigastrium, mid-clavicular line and anterior axillary line – the mirror image of positions used in laparoscopic cholecystectomy. Attachments of the splenic flexure of the colon occasionally impede the positioning of the lateral cannula and access of the lienorenal ligament. If so, the splenic flexure is mobilized before insertion of the most lateral cannula. A diathermy hook is placed in the lateral cannula, a suction irrigator in the central cannula and an atraumatic grasper in the epigastric cannula.

The posterior edge of the spleen is elevated and held in this position by the assistant. The lienorenal ligament is divided by means of diathermy, allowing the spleen to become increasingly mobile. Exposure of the lienorenal ligament in the last four patients of the series has been greatly improved by using a 10-mm epigastric cannula (in place of the 5-mm cannula), to provide access for a 'Fan' retractor (AutoSuture, Ascot, UK) during this dissection. It is important to continue this dissection as far superiorly as possible, as high posterior adhesions to the diaphragm are difficult to divide at a later stage. The hilar vessels and the tail of the pancreas come into view and are protected The spleen is placed back in its bed and the anterior edge is elevated. In most cases no adhesions are present, but some dissection may be required if there are non-anatomical adhesions to the stomach. Omental adhesions, often present at the lower splenic pole, are not suitable for diathermy as they may contain sizeable vessels. They should be divided between clips if they are impeding elevation of the spleen, or incorporated within the jaws of the stapler during division of the hilar vessels. Great care is taken during the dissection not to breach the splenic capsule as this may cause troublesome bleeding and the risk of splenic autotransplantation. Minor bleeding is controlled by suction irrigation and diathermy. Secure haemostasis is achieved as the hilum is cross-stapled and this remains the primary objective of the dissection at all times.

By placing a retractor on each side of the hilar structures, the spleen can be elevated (*Fig. 1a*) and the thickness of the hilum estimated Although the best angle of approach for the stapler to

Paper accepted 23 April 1996

the hilum is most often via the mid-clavicular cannula, in some cases the lateral cannula is more appropriate. The chosen 5-mm cannula is replaced with one of 15 mm and a powered vascular linear stapler (Endo-GIA60; AutoSuture) is inserted, opened and carefully positioned across the hilum. The instrument can be closed without firing so that it can be repositioned without difficulty. Once positioned, abutting the spleen and encompassing the hilar vessels (*Fig. 1b*), the stapler is fired, opened and carefully withdrawn. The spleen is now attached only by the short gastric vessels and is highly mobile. A second and third firing of the stapler may be required to complete the separation of the spleen. A shorter 30-mm stapler has been tried but required more firings and was no easier to manipulate into position.

A large retrieval bag is inserted via the 15-mm cannula and the spleen is manipulated into it. Saline irrigation is performed and the splenic bed, omentum and mesentery are examined for splenunculi. None was found in this series. The bag is withdrawn and the spleen is removed piecemeal after morselation with sponge holding forceps. In cases where the spleen is required intact for histological examination, or if it is too large to be placed in a retrieval bag, a small Pfannenstiel incision is made to retrieve the organ. A suction drain is placed in the splenic bed through the most lateral cannula. Bupivacaine 0·5 per cent with adrenaline 1:200000 is infiltrated into the wounds (total volume 20 ml). The 15-mm cannula site is closed in layers with 2/0 polyglactin and subcuticular 3/0 polyglactin to the skin. The 5-mm incisions are closed with sterile skin closure strips.

Postoperative care. The patient is allowed to eat and drink on recovery from the anaesthetic, usually on the evening of surgery. Completion of splenectomy was assessed at operation and by the patient's clinical course after operation. Isotope scans have not been required to detect residual splenunculi.

Results

In the two patients with lymphoma there was massive splenomegaly; the retrieved spleen weighed 1·5 and 2·5 kg. The patient with chronic lymphocytic leukaemia also had a spleen weighing more than 1 kg which was not suitable for laparoscopic dissection. These organs would have been irretrievable even if the laparoscopic dissection had been successful; two of these patients underwent open surgery without laparoscopy. One patient with autoimmune haemolytic anaemia had undergone previous transperitoneal aortic aneurysm surgery and, although laparoscopy was safely performed, dense adhesions forced early conversion to open surgery.

Laparoscopic evaluation was performed in 26 patients and splenectomy was attempted in 25. The spleen was successfully mobilized and separated in 23 patients. In one case the hilar vessels were damaged by accidental injury with the Endo-GIA stapler and subsequent bleeding forced conversion. The second patient, who had acquired immune deficiency syndrome (AIDS), proved to have a markedly thickened hilum which could not be safely thinned to allow application of the stapler. In the remaining 23 patients the operation was completed entirely laparoscopically in 18 and open retrieval was performed in five cases, three for suspected lymphoma and two because the spleen was too large to fit into the retrieval bag.

Two patients in the first half of the series required early reoperation for bleeding. In the first, a postoperative heparin infusion (to protect a prosthetic mitral valve) was associated with bleeding from a small artery close to the staple line. In the second patient with AIDS, hepatitis B and C, and related hepatic cirrhosis, the site of bleeding was not identified but a good recovery was made following evacuation of the haematoma.

There were no infective complications following surgery. One patient, admitted 23 days after surgery with a proven pulmonary embolus, was treated by anticoagulation. There were no other perioperative complications.

The mean time from induction of anaesthetic to transfer to the recovery area was 137 (range 40–260) min, falling from 175 min for the first 11 operations to 105 min for the last 14. Uncomplicated patients (those with idiopathic thrombocytopenia and autoimmune haemolytic anaemia) treated entirely laparoscopically were discharged a median of 3 (range 1–5) days after operation and those with HIV infection or AIDS with more complex associated problems left hospital after 5 (range 2–8) days.

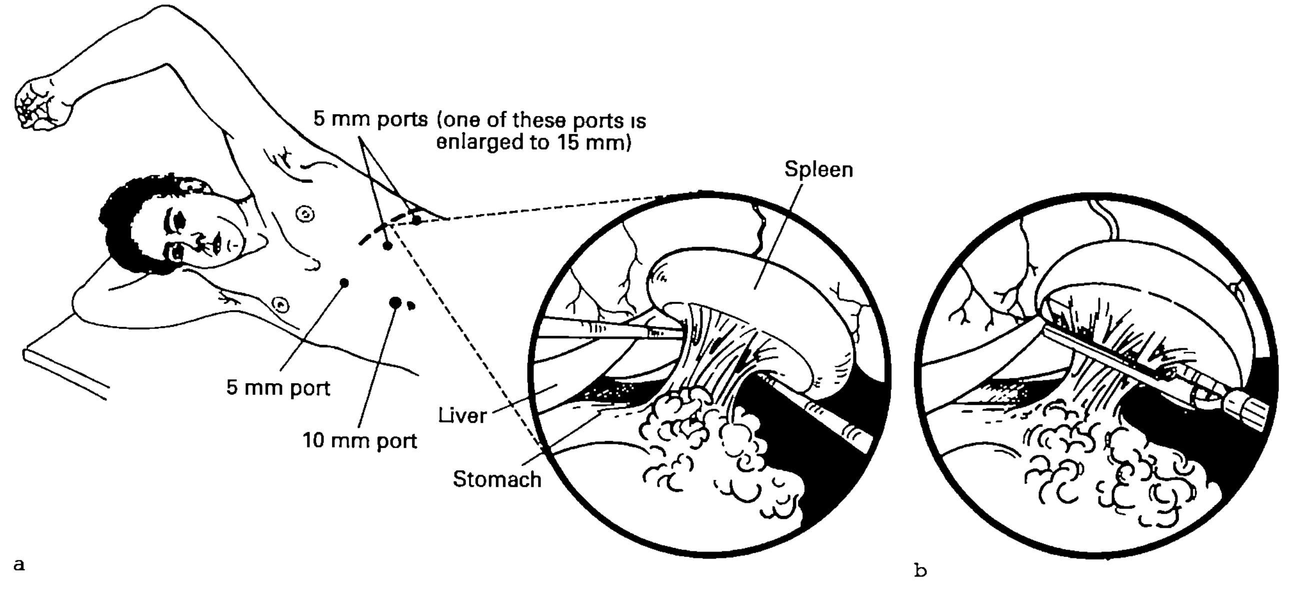

Fig. 1 a Port-site positions with the patient in the semi right-lateral position, allowing mobilization and elevation of the spleen (inset). b The powered vascular linear stapler is placed across the hilum of the spleen, closed and fired

Patients who required open retrieval were discharged a median of 6 (range 2–13) days after surgery. There was no postoperative mortality.

Discussion

The most common indication for elective splenectomy is thrombocytopenia[11–15], which may be HIV related[16–19]. Mortality has been reported following splenectomy in patients with AIDS[20]. A secondary concern during AIDS-related surgery is exposure of the surgeon to the patient's body fluids[21]. Both the patient and the surgical team may therefore benefit from a minimal access approach.

Using this technique, the authors have found laparoscopic splenectomy to be a technically feasible operation which may be performed within a reasonable operating time. This approach, when successfully completed, has led to a reduction in hospital stay, even in patients with AIDS. The benefits, in terms of reduction of hospital stay, are similar to those achieved by laparoscopic cholecystectomy[22].

Problems associated with this technique have been related to its development and occurred in the first half of the series. In particular, the procedure requires safe handling techniques for the spleen using laparoscopic instruments and the use of the powered vascular linear stapler. Considerable skill is required in the safe elevation and mobilization of the spleen, particularly when it is large. Preoperative splenic artery embolization and early clipping of the splenic artery via a posterior gastric approach have been advocated to reduce operative blood loss[23,24]. The technique described here has overcome the problem of blood loss without the need to utilize either of these techniques.

Spleens that are bigger than the largest retrieval bag, or that are required whole for pathological examination, require an open retrieval which can be achieved through a Pfannenstiel incision. The present results with this technique compare well with others[25]. Although single-handed mobilization of the spleen through a Pfannenstiel incision has been described by Kusminsky *et al.*[26], a procedure that has obvious advantages for patients with larger spleens, this was not attempted in any of the present patients.

Elective splenectomy is a relatively uncommon procedure which can be performed laparoscopically, although this requires considerable technical expertise. The authors would recommend that this procedure be performed in a limited number of specialist centres to maximize the experience gained by laparoscopic surgeons. This technique is reliable, associated with low morbidity and can be performed in an acceptable time.

In conclusion, laparoscopic splenectomy offers a considerable reduction in postoperative morbidity, similar to that associated with laparoscopic cholecystectomy. The operation may be performed with the minimum of specialist instrumentation by appropriately trained laparoscopic surgeons.

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British Journal of Surgery 1996, 83, 1215–1218

Changing management of pyogenic liver abscess

R. RINTOUL, M. G. O'RIORDAIN, I. F. LAURENSON*, J. L. CROSBIE,
P. L. ALLAN† and O. J. GARDEN

*University Departments of Surgery, *Medical Microbiology and †Radiology, The Royal Infirmary, Edinburgh EH3 9YW, UK*
Correspondence to. Mr O. J. Garden

The case records of 23 patients who presented over a 5-year period with a diagnosis of pyogenic liver abscess were reviewed. Ascending cholangitis was implicated in nine cases, seven of which were associated with underlying malignancy. Haematogenous spread via the portal route accounted for five cases. Primary treatment included percutaneous abscess drainage in 15 patients. Whereas nine of the 11 patients with benign underlying pathology were managed successfully, the four with malignant biliary obstruction did not survive. Only one of the 23 patients who presented with hepatic abscess required surgical intervention. Percutaneous abscess drainage combined with appropriate antibiotic therapy is an effective means of managing hepatic abscess, but there remains a substantial overall mortality rate resulting from the increasing incidence of malignant biliary obstruction as a cause of this condition.

The incidence of pyogenic liver abscess has remained relatively constant during this century despite earlier diagnosis and treatment of underlying causes and more aggressive antibiotic therapy[1–3]. In recent years the decrease in cases resulting from haematogenous spread from infective foci has been mirrored by an increase in cases secondary to hepatobiliary pathology[1,3]. In particular, advances in the management of hepatobiliary malignancy have led to increased survival times and pyogenic liver abscess is more commonly being seen as a complication following percutaneous or endoscopic management of biliary obstruction[4]. In the past, traditional treatment of liver abscess comprised antibiotic therapy and surgical drainage but, more recently, the role of percutaneous drainage in the management of this condition has been emphasized[5–8].

A review was carried out of the present authors' experience of pyogenic liver abscess to examine the aetiology and to determine the effectiveness of the management policy of percutaneous drainage as the mainstay of treatment for such patients.

Patients and methods

The case records of patients with a discharge diagnosis of pyogenic liver abscess who were admitted to the hepatobiliary surgical unit of Edinburgh Royal Infirmary between January 1989 and December 1993 were reviewed. A computerized search of appropriate discharge diagnosis codes was made and cross-referenced with a similar search of microbiological records. Twenty-three patients were identified for this 5-year period, of whom 16 had been transferred from other centres. Patients who had been admitted to the unit with cholangitis and occlusion of stents were not included in the study if, at the time of repeat endoscopic retrograde cholangiography, small abscesses were shown to be communicating with the biliary tree.

Diagnosis was made by a combination of clinical findings, visualization of abscess by ultrasonography or computed tomography (CT), aspiration of purulent material from the radiological abnormality and post-mortem examination. Specimens were collected in a sterile container and sent for immediate aerobic and anaerobic culture. Patients with amoebic abscess were excluded. Using a standard pro forma, patient demographic details, presenting symptoms and signs, haematological and biochemical results, microbiological findings, diagnostic method findings, abscess characteristics, aetiology, treatment and final outcome were documented.

Before microbiological identification from blood and/or drain cultures, broad-spectrum antibiotics were often administered. These were modified when sensitivities became known. Percutaneous drainage of collections larger than 5 cm was normally undertaken using ultrasonography for initial guidance. Puncture was done using a 16-G needle–catheter assembly followed by fluoroscopy for the insertion and manipulation of appropriate drains using a Seldinger technique. Smaller collections, or those where access was difficult, were punctured initially with a 22-G needle through which a 0·18-inch guidewire (Neff Set; Cooks, Letchworth, UK) was passed. Subsequent exchanges allowed placement of a 0·89- or 0·97-mm guidewire, along which a drain of appropriate size was inserted. Percutaneous aspiration alone was used when small multiple abscesses were demonstrated. If biliary obstruction was demonstrated, percutaneous or endoscopic drainage of the biliary tree was subsequently undertaken. Drains were left in place until resolution of symptoms and signs, until drainage ceased or until the abscess was shown to have resolved on scanning and/or by tubography. Surgical drainage or hepatic resection was reserved for chronic hepatic sepsis unresponsive to non-operative treatment.

Results

Of the 23 patients, 17 were men. The median age was 62 (range 23–80) years. Fever, abdominal pain and tenderness were the most prevalent symptoms and signs at the time of diagnosis (*Table 1*). The duration of symptoms before hospital admission ranged from 1 day to 6 months. For the 20 patients who had pyogenic liver abscess at the time of hospitalization, the median delay to diagnosis was 4 (range 1–21) days.

Significant haematological and biochemical abnormalities are presented in *Table 2*. Serum albumin concentration was measured in 17 patients and found to be below the normal range (less than 35 g/l) in 16. C-reactive protein levels were raised in all nine patients in whom it was measured (median 10·3 (range 3·4–20·8) mg/dl; normal value less than 1·0 mg/dl).

All 23 patients underwent ultrasonography or CT. Ultrasonography was used in 21 patients and failed to detect abscesses in only two, in whom their presence was suspected clinically. Of these two patients, an abscess was subsequently found by CT in one and at autopsy in the

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Paper accepted 10 December 1995

Table 1 Symptoms and signs noted in 23 patients at the time of diagnosis of liver abscess

	No. of patients
Symptoms	
Abdominal pain	14
Fever	12
Jaundice	8
Anorexia	7
Nausea and/or vomiting	7
Malaise	7
Signs	
Pyrexia (> 37·5°C)	17
Abdominal tenderness	13
Hepatomegaly	8
Jaundice	8
Cachexia	7

Table 2 Abnormal laboratory findings in 23 patients with liver abscess at the time of diagnosis

	No. of patients
Haemoglobin < 12 g/dl	15
White cell count > 11 000 × 10^9/l	13
Alkaline phosphatase > 100 units/l*	23
γ-Glutamyl transpeptidase > 55 units/l†	22
Alanine aminotransferase > 40 units/l‡	17

Normal ranges: *40–100, †10–55 and ‡10–40 units/l

other. CT was used as the first-line imaging investigation in two patients, and an abscess was seen on both occasions. Biliary dilatation was not a prominent feature on either ultrasonography or CT in patients with known or suspected biliary pathology.

Abscess morphology and microbiology

Single abscesses were found in eight patients and multiple abscesses in 15. Abscesses were restricted to the right lobe in 17 cases and occurred in both lobes in six. There were no cases of the left lobe being involved alone. The abscess ranged in size from 1 to 16 cm.

Sixteen of the 23 patients had positive blood cultures. Of the 21 patients who had pus aspirated or drained from abscesses, 16 had positive cultures. Overall, of the 20 patients with positive cultures, 11 were polymicrobial; only two of these patients had received antibiotics before admission to hospital. None of the three patients with negative cultures had taken antibiotics before hospital admission. The most commonly identified groups of organisms were Enterobacteriaceae, *Streptococcus milleri* and enterococci (*Table 3*). Only three of 37 isolates were anaerobes.

Aetiology

A cause for abscess formation was identified in 20 patients. Ascending cholangitis was implicated in nine cases, seven of which were associated with malignancy. Overall, hepatic causes accounted for three abscesses and haematogenous spread via the portal route for five. No cause was found in three cases (*Table 4*).

Table 3 Organisms identified in 20 patients with hepatic abscess in whom cultures were positive

	No. of patients
Aerobes	
Gram-positive	
Staphylococcus aureus	3
Methicillin-resistant *S. aureus*	1
Streptococcus milleri	7
Enterococcus spp.	5
Enterococcus faecium	2
Enterococcus faecalis	2
Gram-negative	
Enterobacteriaceae	
Klebsiella sp.	1
Escherichia coli	8
Serratia marcescens	1
Hafnia alvei	1
Pseudomonas aeruginosa	2
Anaerobes	
Gram-positive	
Clostridium sp.	1
Clostridium perfringens	1
Gram-negative	
Bacteroides sp.	1
Fungi	
Candida albicans	1

Table 4 Aetiology of hepatic abscess in 23 patients

	No of patients
Biliary obstruction with ascending cholangitis	
Cholangiocarcinoma	4
Pancreatic carcinoma	3
Choledocholithiasis	1
Iatrogenic stricture	1
Hepatic	
Infected metastases	2
Inflammatory pseudotumour	1
Local extension	
Acute cholecystitis	2
Portal	
Diverticular disease	2
Chronic pancreatitis	2
Duodenal ulcer	1
Chronic granulomatous disease	1
Idiopathic	3

Management

All 23 patients received broad-spectrum antibiotics. In four patients this comprised the only medical treatment. Fifteen patients underwent percutaneous abscess drainage. In the others the only intervention was decompression of the biliary tree, one by percutaneous drainage, the other by endoscopic drainage. One patient was treated by operation. In one patient the diagnosis was made as an incidental finding at autopsy, the cause of death having been shown to be due to uncontrolled sepsis secondary to suppurative cholecystitis.

Medical treatment

Of the four patients treated with antibiotics alone, three had undergone diagnostic percutaneous needle aspiration of the abscess. Diagnostic aspiration was chosen in these cases rather than percutaneous abscess drainage because of the multiplicity of small lesions unsuitable for drain insertion. In no case was there clinical or radiological evidence of obstruction of the biliary tree. The two patients with underlying benign pathology (gallstones, one; chronic pancreatitis, one) survived whereas the two with carcinomatosis died in hospital. The patient with gallstones subsequently underwent open cholecystectomy on a second admission and was found to have common bile duct stones which were dealt with by exploration of the common duct.

Biliary tree decompression

Two of the patients who had developed multiple abscesses as a result of malignant obstruction required biliary decompression in addition to antibiotic therapy. One patient underwent initial percutaneous biliary drainage followed by internalization of the stent and the other had endoscopic placement of a biliary stent. In both instances, the abscesses resolved without the need for direct abscess drainage.

Percutaneous abscess drainage

Fifteen of the 23 patients underwent percutaneous abscess drainage (PAD) as the primary treatment. Of this group of 15, four had underlying malignancy and 11 had a benign pathology. There was only one postprocedural complication, a self-terminating episode of haemorrhage into the percutaneously placed drain. All four patients with malignant pathology had some degree of abscess resolution with drainage and antibiotic therapy but, despite repeated attempts to improve biliary drainage by endoscopic or percutaneous means, all four developed recurrent abscesses and died from a combination of sepsis and progression of tumour within 1 year of initial presentation.

Of the 11 patients with abscesses due to a benign cause, nine had complete resolution of the abscess by PAD and antibiotic therapy. Of the two patients who developed recurrent abscess formation, one died from chronic granulomatous disease and the other required a right hepatectomy to remove an inflammatory pseudotumour. In this latter patient, the abscess recurred several months after apparently successful percutaneous drainage. CT had demonstrated an inflammatory mass in the posterior sector of the liver which did not settle after repeat percutaneous drainage. A further patient in this group with a benign cause subsequently underwent laparoscopic cholecystectomy, the previously resolved abscess having been demonstrated to communicate with the gallbladder.

Surgical drainage

One patient who had developed a hepatic abscess secondary to obstructing pancreatic carcinoma underwent surgical drainage of the abscess and decompression of the biliary tree by means of hepaticojejunostomy. Previous attempts at endoscopic biliary stenting before referral had been unsuccessful. The hepatic abscess resolved and the patient was successfully discharged from hospital.

Outcome

Eight patients died in hospital. Only three of the nine patients with underlying malignancy were successfully discharged from hospital. There were two deaths in the 14 patients with non-malignant disease. In one of these patients the underlying pathology was chronic granulomatous disease. The other death was a result of overwhelming sepsis secondary to suppurative cholecystitis. In this patient, who died within 24 h of admission, pyogenic liver abscess was an incidental finding at autopsy.

Discussion

The mean age of patients with pyogenic liver abscess has shown a progressive rise over the past few decades[1,5,6]. In this study the median age of patients at presentation was 62 years. This trend is primarily a reflection of the changing aetiology of pyogenic liver abscess, as in the past haematogenous spread from distant infective foci was common[1]. Several other recent series mirror the present experience in demonstrating that ascending cholangitis as a result of biliary obstruction primarily due to malignant disease is now the main cause of liver abscess in the non-immunosuppressed patient[5,7–9].

CT is advocated as being more sensitive than ultrasonography[10], but the latter is still the first-line investigation in the authors' centre, even though it is accepted that this technique is operator dependent and may not adequately exclude the presence of other abscesses. Although certain areas of the liver may be difficult to visualize by ultrasonography and results can be limited by technical factors[10], ultrasonography is undoubtedly cheaper and does not use ionizing radiation. It also enables real-time guidance of drainage procedure in the majority of cases. The ready availabiliy of ultrasonography also assists in decreasing the delay in diagnosis. None the less, CT was useful in one patient in the present study when ultrasonography failed to detect obvious hepatic sepsis, and it may be useful in assisting to differentiate malignant from benign abscess formation. Fine-needle aspiration may be needed to clarify the diagnosis in some patients, but some authors have advocated isotope scanning, cholangiography and selective angiography[3,11]. These investigative modalities are largely redundant and were not used in any patient in the present series. They have been superseded by non-invasive imaging techniques such as ultrasonography, CT and, more recently, magnetic resonance imaging.

Enterobacteriaceae, enterococci, *Streptococcus milleri* and anaerobes are common gastrointestinal tract isolates, and were all identified in the liver abscesses in the present series. Whereas the pattern of aerobic infection is similar to that of other reported series, the relatively low incidence of anaerobic infection compared with that in other series may be a reflection of specimen collection techniques[3,11]. Fine-needle aspiration with rapid handling and anaerobic incubation is important for the isolation of anaerobes. Minimum delay between specimen collection and anaerobic incubation is necessary to optimize the recovery of anaerobes. In this series cultures from 11 of 20 patients were polymicrobial and this too accords with a gastrointestinal origin.

Currently both percutaneous needle aspiration and PAD in conjunction with antibiotics are advocated as alternatives to surgery in the management of pyogenic liver abscess when immediate surgery is not required to deal with coexistent intra-abdominal pathology[7,12,13]. Percutaneous therapy offers a low-risk approach to often critically ill patients and achieves effective drainage without the need for general anaesthesia and surgery. There is current debate in the literature over the comparative efficacies of non-surgical treatment[5,7,8,11,14,15]. Though a combination of antibiotic therapy and PAD is thought to be more effective, there are to date no controlled trials comparing this with antibiotic therapy and diagnostic fine-needle aspiration. The latter technique provides material for both histological and bacteriological analysis when there is doubt regarding the aetiology of the abscess. Irrespective of whether PAD or percutaneous needle aspiration was undertaken in the present series, patients with underlying malignancy fared badly.

Only one patient underwent surgical drainage of an abscess as a primary procedure, whereas another, whose abscess recurred despite repeated PAD, underwent right hepatectomy to remove an inflammatory pseudotumour evident on CT. The proportion of patients in the present series who underwent immediate surgery was low compared with that in other reports[5,6]. When percutaneous drainage was initially introduced for the management of hepatic abscess, morbidity and failure rates were equal or greater to those obtained at surgery[5,6], but with increasing experience failure rates of PAD appear to have fallen[16]. Although percutaneous drainage failed in six of 15 patients in the present series, this was undoubtedly biased by the high proportion with underlying malignancy who were not obvious candidates for surgical intervention.

PAD combined with appropriate antibiotic therapy appears to be the treatment of choice, given its higher success and low complication rates. The procedural complication rate of one in 15 compares favourably with published complication rates of 4–20 per cent[5,12]. There were no deaths directly attributable to the drainage procedure in the present series and clearly a percutaneous approach is more appropriate for patients with extensive carcinomatosis in whom cure is unlikely. However, in this latter group, effective biliary drainage is as important as abscess drainage if sepsis is to be adequately controlled. This was emphasized by the two patients with pyogenic liver abscess secondary to malignant obstruction of the biliary tree in whom sepsis resolved with a combination of biliary decompression and antibiotic therapy alone. On the other hand, four other patients who underwent direct abscess drainage but had unrelieved biliary obstruction died in hospital.

The mortality rate of two of 14 patients with non-malignant disease, similar to that of other recent series[5,7,12] demonstrates that the prognosis for a patient with pyogenic liver abscess has much improved over the past 15 years. This appears to be due to a combination of more rapid diagnosis as a result of improved radiological imaging, more effective antibiotic therapy and the development of percutaneous drainage procedures. The prognosis, however, for patients with pyogenic liver abscess with underlying hepatobiliary malignancy remains poor and will continue to provide a challenge in the future.

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British Journal of Surgery 1996, 83, 1219–1222

Recurrence of hepatocellular carcinoma after surgery

J. YAMAMOTO, T. KOSUGE, T. TAKAYAMA, K. SHIMADA, S. YAMASAKI, H. OZAKI, N. YAMAGUCHI* and M. MAKUUCHI†

*Department of Surgery, National Cancer Centre Hospital, *Epidemiology Division, National Cancer Centre Research Institute and †Second Department of Surgery, Tokyo University School of Medicine, Tokyo, Japan*
Correspondence to: Dr J. Yamamoto, Department of Surgery, National Cancer Centre Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104, Japan

A total of 386 patients who underwent complete resection of hepatocellular carcinoma over an 8-year period were assessed retrospectively for tumour recurrence. Some 219 (56·7 per cent) of the patients developed recurrence. Patients with a greater degree of cirrhosis showed a longer interval to recurrence; the median (range) interval until recurrence was 7·9 (1·8–84·2) months in patients with a normal liver, 13·4 (2·0–79·5) months in those with chronic hepatitis and 16·7 (1·5–73·1) months in those with cirrhosis. Intrahepatic recurrence was observed more frequently in either the same (26·4 per cent) or the adjacent (24·8 per cent) Healey segment than in the lobe contralateral to the primary tumour (17·8 per cent). The presence of portal venous invasion and/or intrahepatic metastasis, underlying liver cirrhosis and perioperative blood transfusion were determined to be independent predictors of recurrence by multivariate analysis. Because intrahepatic spread of hepatocellular carcinoma occurs in a segment-by-segment manner, surgeons should use an anatomically wide resection within the hepatic functional reserve.

Recent advances in surgical techniques for liver resection have made operation a safe and effective treatment for hepatocellular carcinoma (HCC), and the survival rate of patients with hepatoma after curvative resection has been reported to exceed 50 per cent[1]. However, even if the resection is curative, recurrence is frequently encountered, especially in the residual liver, within a relatively short period after operation[2–7]. Early spread via the portal venous system as well as possible multicentric carcinogenesis of HCC, especially in the cirrhotic liver, limits the potential for surgical cure of hepatoma[8]. This study examined patients who underwent complete resection for HCC over an 8-year period and assessed post-resection recurrence to determine a rational surgical protocol for the disease.

Patients and methods

Between 1984 and 1991, 492 patients underwent primary hepatic resection for HCC at the National Cancer Centre Hospital in Tokyo. Twelve patients (2·4 per cent) died within 1 month of surgery or during the initial hospital stay. In 94 patients (19·1 per cent) the resection was incomplete. Of these, 23 patients had exposed non-encapsulated tumours, 11 had ruptured encapsulated tumours, 18 had a positive surgical margin due either to portal tumour thrombus or at the site of intrahepatic metastasis, 36 underwent debulking resection only because of limited liver function, and four had extrahepatic disease. The case records of the remaining 386 patients were reviewed. After operation patients were followed every 3 months by measurement of serum α-fetoprotein (AFP) levels, ultrasonography, computed tomography and, if necessary, hepatic angiography. Recurrence was defined clinically as new lesions with features of HCC by more than two imaging methods[9]. The distribution of intrahepatic recurrence in relation to the main tumour at the primary resection was classified on the basis of segmental liver anatomy as follows: (1) segmental, when the tumour recurred in the same Healey segment[10]; (2) ipsilobar, in the segment adjacent to the resected primary lesion in the ipsilateral lobe; (3) contralobar, in the lobe contralateral to the resected primary lesion; (4) bilobar, in both lobes; and (5) diffuse, diffusely as numerous foci throughout the whole remnant liver. The follow-up period ranged from 2·1 to 111·3 (median 38·8) months. Patients without recurrence were followed for at least 6 months after surgery.

The following factors were analysed with reference to their prognostic significance in recurrence: age, sex, status of hepatitis virus infection, associated liver cirrhosis, hepatic reserve according to the Child classification, serum AFP level, operative blood loss, perioperative blood transfusion (either during surgery or within 1 week afterwards), surgical procedure, the number and size of the tumour(s), presence of portal venous invasion and/or intrahepatic metastasis, presence of a fibrous tumour capsule, width of the tumour-free margin, and Edmondson–Steiner's histological grading The surgical procedure was defined according to the segmental anatomy of the liver: lobectomy, resection of a hemihepatic lobe; segmentectomy, resection of a segment according to Healey's definition; subsegmentectomy[11], resection of Couinaud's segment[12]; limited resection, all other forms of non-anatomical resection less extensive than segmentectomy. Recurrence rates were calculated by the Kaplan–Meier method and differences between recurrence curves were assessed with the log rank test. The Cox proportional hazards model was used to determine the variables most significantly related to disease recurrence[13].

Results

Clinicopathological data at primary resection

Men outnumbered women by 311 to 75, and the mean age was 59·7 (range 19–80) years. Some 362 patients (93·8 per cent) had histologically proven chronic liver disease, including 229 (59·3 per cent) with cirrhosis and 133 (34·5 per cent) with chronic hepatitis. The serum level of AFP ranged from 2·5 to 749 626 (mean 450) ng/ml. Some 294 patients (76·2 per cent) had a solitary tumour. The mean maximum diameter of the tumours was 4·2 (range 0·9–26) cm. Microscopic portal venous invasion and/or intrahepatic metastases were found in 186 patients (48·2 per cent) and the tumour had a fibrous capsule in 327 (84·7 per cent). The surgical procedure was limited hepatic resection in 223 patients (57·8 per cent), subsegmentectomy in 70 (18·1 per cent), segmentectomy

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Paper accepted 14 December 1995

in 46 (11·9 per cent) and lobectomy in 47 (12·2 per cent). Mean operative blood loss was 1015 (range 40–7500) ml and 85 patients (22·0 per cent) received blood transfusion during the operative period.

Patients with recurrence

Among the 386 patients, 219 (56·7 per cent) developed recurrence during the follow-up period of 1·5–84·2 (median 38·2) months. Of these 219 patients, tumour recurrence was confined to the remnant liver in 189 (86·3 per cent). Both intrahepatic and extrahepatic recurrence of the tumour was recognized in 19 patients. In 11 patients only extrahepatic organs were involved: lung (four patients), bone (three), lung and brain (one), lung and peritoneum (one), bone and lymph node (one), and bone and pharynx (one).

Time to recurrence

Among the 189 patients who developed recurrence in the liver only, 128 (67·7 per cent) did so during the first 2 years after surgery. Nine of 10 patients with a normal liver had intrahepatic recurrence within 2 years after resection, whereas in those with cirrhosis 47 (35·3 per cent) of 133 developed recurrence confined to the liver after 2 years (*Fig. 1*). The median (range) time to recurrence in relation to the state of the non-cancerous liver parenchyma was 7·9 (1·8–84·2) months in patients with a normal liver, 13·4 (2·0–79·5) months in those with chronic hepatitis, and 16·7 (1·5–73·1) months in those with cirrhosis.

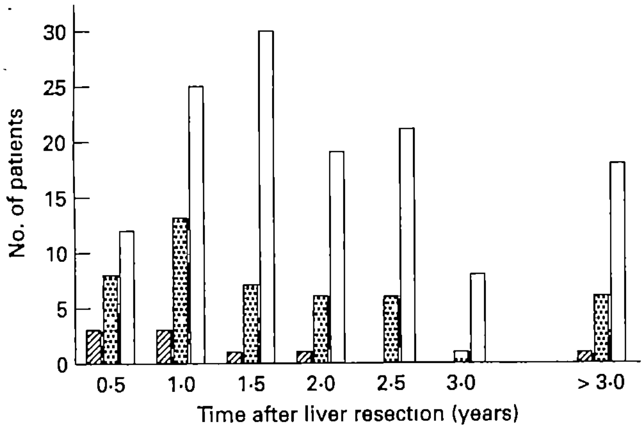

Fig. 1 Time course of the incidence of intrahepatic recurrence according to the state of non-cancerous liver parenchyma in 189 of 386 patients who underwent liver resection. ▨, Normal liver; □, chronic hepatitis; □, cirrhosis

Table 1 Distribution of intrahepatic recurrence in relation to the main tumour at primary resection classified on the basis of segmental liver anatomy

	Recurrence confined to the liver	Resection less extensive than segmentectomy for solitary HCC
Segmental	46 (24·3)	34 (26·4)
Ipsilobar	46 (24·3)	32 (24·8)
Contralobar	42 (22·2)	23 (17·8)
Bilobar	21 (11·1)	20 (15·5)
Diffuse	21 (11·1)	15 (11·6)
Not known	13 (6·9)	5 (3·9)
Total	189 (100)	129 (100)

Values in parentheses are percentages. HCC, hepatocellular carcinoma

Mode of intrahepatic recurrence

Of the 189 patients in whom recurrence was confined to the liver, one-quarter had recurrence in the same Healey

Table 2 Univariate analysis of prognostic factors for recurrence of 386 resected hepatomas

Factor	No. of patients	Disease recurrence rate (%) 1 year	3 years	5 years	*P**
Overall		21·8	61·5	74·1	
Age (years)					
<60	190	24·3	63·9	75·0	0·77
≥60	196	19·8	59·1	75·7	
Sex					
M	311	19·9	61·2	73·7	0·60
F	75	31·3	62·5	75·7	
Hepatitis B virus antigen					
Negative	315	22·5	62·5	77·2	0·15
Positive	68	21·1	59·7	71·8	
Hepatitis C virus antibody					
Negative	90	22·2	60·9	84·4	0·28
Positive	155	23·7	63·6	91·1	
Non-cancerous liver parenchyma					
No cirrhosis	157	23·8	49·2	58·3	0·0009
Cirrhosis	229	20·4	70·3	83·2	
Child classification					
A	265	18·1	57·1	69·9	0·002
B or C	121	29·6	72·4	87·5	
Serum α-fetoprotein (mg/ml)					
<400	306	19·1	62·4	83·0	0·14
≥400	71	35·9	63·3	88·3	
Operative blood loss (ml)					
<1000	231	18·4	59·2	69·9	0·11
≥1000	155	26·6	64·6	70·6	
Perioperative blood transfusion					
No	301	19·5	58·2	71·5	0·001
Yes	85	29·5	71·9	86·8	
Surgical procedure					
Limited resection	223	21·0	65·5	80·2	n.s.
Subsegmentectomy	70	17·0	57·8	73·2	
Segmentectomy	46	19·0	48·6	64·4	
Lobectomy	47	36·3	62·8	62·8	
No. of tumours					
Solitary	294	19·8	57·1	70·2	0·001
Multiple	92	26·8	77·2	90·2	
Size of tumour (cm)					
<5	285	18·1	62·3	74·7	0·75
≥5	101	32·2	58·8	71·2	
Presence of portal venous invasion and/or intrahepatic metastasis					
Absent	200	10·1	49·9	67·2	0·0001
Present	186	34·6	74·5	84·0	
Fibrous capsule					
Absent	59	16·2	53·5	82·8	0·32
Present	327	22·8	63·6	75·3	
Distance of tumour-free margin (mm)					
<10	317	22·0	60·5	74·4	0·96
≥10	69	21·4	63·3	85·3	
Histological grading by Edmondson and Steiner's classification					
I or II	250	17·9	64·9	78·1	0·95
III or IV	94	34·2	59·9	73·4	

*The significance of the difference for each parameter was tested by the log rank test modified for censoring; n.s., not significant segment. Other ipsilobar recurrence was also seen in a further one-quarter of the patients. Considering only the 129 patients with a solitary tumour who underwent resection less extensive than segmentectomy, the tumour recurred three times more frequently in the ipsilateral than in the contralateral lobe (*Table 1*).

Analysis of factors predictive for recurrence

When the cumulative recurrence rate was compared among the various subgroups identified by each predictive factor, associated liver cirrhosis, poor hepatic reserve (Child grade B or C), multiple tumours, presence of portal venous invasion and/or intrahepatic metastasis, and perioperative blood transfusion were found to be significantly related to a shorter time to recurrence (*Table 2*). However, the prognostic variables shown to be significant by multivariate analysis were portal venous invasion and/or intrahepatic metastasis, liver cirrhosis and blood transfusion (*Table 3*).

Table 3 Significant prognostic factors for recurrence of 386 resected hepatomas

Factor*	*n*	Relative risk of recurrence†	*P*‡
Portal venous invasion and/or intrahepatic metastasis			
Absent (0)	200		
Present (1)	186	1·79 (1·35–2·37)	0·0001
Non-cancerous liver parenchyma			
Not cirrhotic (0)	157		
Cirrhotic (1)	229	1·59 (1·18–2·15)	0·002
Perioperative blood transfusion			
Not performed (0)	301		
Performed (1)	85	1·47 (1·10–1·97)	0·01

*Forward and backward stepwise analyses were used to select these variables. †Relative risks were expressed as the exponential coefficients and reflected increased hazards of the 0-coded factor; values in parentheses are 95 per cent confidence intervals. ‡Cox proportional survival analysis

Survival after recurrence

Of the 219 patients who developed recurrence, 127 (58·0 per cent) died, with a median survival time of 51·7 months. The median survival time after the diagnosis of recurrence was 30·8 months.

Discussion

Despite the improved safety of surgical therapy, recurrence of HCC after surgery remains common. In this study most of the patients who died had recurrence, so the prevention of recurrence is important if overall survival is to improve.

Portal venous invasion and/or intrahepatic metastasis is one of the most important predictive variables for recurrence, as has been reported previously[14,15]. The fact that more than half of all of the observed intrahepatic recurrences were either in the same Healey segment or in the segment contiguous to the primary resected site in the ipsilateral lobe suggests intrahepatic spread of hepatoma in a segment-by-segment manner via the portal venous system[8,11]. Although two reports[2,6] have described a similar pattern of intrahepatic recurrence, they included only a limited number of patients, and in one report local recurrence was defined as including recurrent tumour in the contralateral lobe after hepatic lobectomy[2]. Other surgeons have reported various rates of local recurrence (14–21 per cent)[3,5,7], but they did not define the distribution of recurrence strictly with regard to the anatomy of hepatic segments.

Some authors advocate a wide surgical margin to improve surgical outcome[16–19]. In the present study the presence of a tumour-free margin (more than 10 mm) did not show the prognostic benefit that other authors have reported[15,20]. Considering the possibility of portal system-based spread, complete removal of the portal area containing the tumour might be more important for curative resection than non-anatomical resection with a wide surgical margin. Although the surgical procedure did not significantly influence the frequency of recurrence, this may have occurred because limited hepatic reserve did not permit a resection wide enough to encompass the full extent of the tumour in many patients with cirrhosis. As the authors have previously reported, anatomical hepatic resection provides a better surgical result, especially when the patient has a non-invasive tumour in a non-cirrhotic liver[1].

Recurrent HCC after resection arises either from non-excised cancer or from *de novo* primary tumours. Unarrested carcinogenesis in the cirrhotic parenchyma is thought to be responsible for the *de novo* appearance of multifocal tumours. However, detectable adenomatous hyperplasia, which has been proven to be a precancerous lesion, requires 2 years or more for transformation into HCC[21]. In fact, in the present study a second peak of recurrence was observed at 2–2·5 years after surgery in cirrhotic patients (*Fig. 1*).

The number of tumour(s) and hepatic reserve, which were identified as being significantly associated with a shorter time until recurrence, had no independent prognostic significance because of the overriding effect of other predictors in multivariate analysis.

These results do not support simple wide resection but rather suggest an anatomically extended resection within safe limits. Late recurrence in the form of a second new tumour arising from multicentric foci would appear to warrant repeat surgery[22,23]. It also seems beneficial, with respect to cancer recurrence, to operate on patients with HCC using an approach that minimizes or avoids the need for blood transfusion[24].

Acknowledgements

This study was supported in part by a grant-in-aid for cancer research and for the comprehensive ten-year strategy for cancer control from the Ministry of Health and Welfare of Japan.

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British Journal of Surgery 1996, **83**, 1223–1225

Randomized trial of periportal peritoneal bupivacaine for pain relief after laparoscopic cholecystectomy

D. J. ALEXANDER, S. S. NGOI, L. LEE, J. SO, K. MAK, S. CHAN and P. M. GOH

Department of Surgery, National University Hospital, Singapore
Correspondence to. Mr D. J Alexander, Department of Surgery, York District Hospital, Wigginton Road, York YO3 7HE, UK

The aim of this study was to determine whether injection of a long-acting local anaesthetic, in relation to the port sites at the level of the parietal peritoneum, would reduce postoperative pain following laparoscopic cholecystectomy. Patients were entered into a randomized, prospective, double-blind study comparing the effects of a standard technique, in which bupivacaine (total of 20 ml, 0·5 per cent) was injected into the subcutaneous periportal tissue around the four port sites, and a technique in which bupivacaine (total of 20 ml, 0·25 per cent) was injected into the subcutaneous periportal tissue as above with the addition of periportal parietal peritoneal injection of bupivacaine (total of 20 ml, 0·25 per cent). Two scores for pain, with the patient at rest, and on movement, were assessed 6 and 18 h after surgery using a visual analogue pain scale. Median pain score was significantly higher in patients who received standard technique ($n = 40$) than in those given peritoneal injection ($n = 40$) at both 6 (rest = 3·0 *versus* 1·0, movement = 5·0 *versus* 2·9) and 18 h (rest = 1·9 *versus* 0, movement = 3·2 *versus* 1·2). Both opiate and oral analgesic requirements were reduced in patients administered peritoneal injection, although this was not statistically significant. The addition of periportal injection of bupivacaine at the level of the parietal peritoneum, performed under direct vision, reduces pain after laparoscopic cholecystectomy.

Day-case cholecystectomy is established[1], because of the reduction in postoperative pain associated with the laparoscopic approach[2]. There is still a significant degree of abdominal discomfort in the immediate postoperative period[3,4]. Postoperative pain is localized to the epigastrium and right upper quadrant, in direct relation to the port sites and the area between them. This pain is not abolished by periportal subcutaneous injection of long-acting local anaesthetic. Trauma to the parietal peritoneum at the port sites may be responsible for postoperative pain. The purpose of this study was to determine whether an additional injection of long-acting local anaesthetic around the port sites, at the level of the parietal peritoneum, would reduce postoperative pain.

Patients and methods

The study comprised a consecutive series of patients who had laparoscopic cholecystectomy by one of three participating consultants at the National University Hospital, Singapore. A standard four-port technique was used with two 11-mm ports placed in the supraumbilical region and epigastrium, and two 5-mm ports in the subcostal area at the mid-clavicular and anterior axillary lines. At the time of induction of general anaesthesia the patients were randomized, using sealed envelopes, to either: (1) standard therapy, in which, after cholecystectomy, a total of 20 ml bupivacaine (0·5 per cent) (Astra Pharmaceuticals, Kings Langley, UK) was injected into the subcutaneous tissue around the four port sites; or (2) peritoneal injection, in which a total of 20 ml bupivacaine (0·25 per cent) was injected around the port entry sites, at the level of the parietal peritoneum, under direct vision using a 23-cm laparoscopic obstetrics and gynaecology needle, of internal diameter 1·5 mm (used for draining ovarian cysts). The injection was considered satisfactory once a bleb had been raised around the port entry site, usually as a result of peritoneal puncture both behind and in front of the trocar. The midline epigastric port and medial right hypochondrial port sites were injected by introducing the needle through the lateral right hypochondrial port. This latter site was injected by introducing the needle through the midline epigastric port. The camera was then removed from the umbilical port which was visualized internally with the camera through the epigastric port. The umbilical port site was injected by introducing the needle through the lateral right hypochondrial port. These patients (peritoneal injection) also received a total of 20 ml bupivacaine (0·25 per cent) in the subcutaneous tissue around the four port sites.

All patients were prescribed postoperative analgesia of oral naproxen sodium (Synflex, (Roche Products, Welwyn Garden City, UK) two 550 mg tablets) and/or intramuscular pethidine (50 mg) as required. Intraoperative opiate analgesia was given at the discretion of the anaesthetist irrespective of the study group, and was recorded prospectively.

Patients were studied at 6 and 18 h after surgery using a visual analogue pain scale (VAPS). A 20-cm grid, without numeration, was constructed and the patient asked to mark a point related to his or her current pain level having been advised that the bottom represented 'no pain' and the top 'worst imaginable pain'. In an effort to standardize this subjective assessment, it was suggested to the patient that a level at the mid-point or greater meant that they were unable to walk unaided. Patients were asked to mark the pain chart at two points at each time of study, referring to level of pain at rest and on movement. The scores were obtained by a 'blinded' independent observer. The patients were unaware of their randomization and this information was kept separate from the notes and operative report. Similarly, the ward nurses were unaware of the randomization and gave out analgesia in the normal way. In most cases the patients were lucid enough to cooperate in the study; however, if there was doubt a simple test was constructed in which the patient was asked to count the number of 'P's in a given sentence. If the patient could not comply, or was asleep, the research assistant returned an hour or two later (thus giving a narrow range to the precise times studied).

Information related to American Society of Anesthesiologists (ASA) grade, operative details, intraoperative and postoperative analgesic consumption, and outcome was collected prospectively.

Comparisons between groups were tested by the Mann–Whitney *U* test, where $P < 0·05$ was considered significant.

Results

Eighty-three consecutive patients were entered into the study. Three were excluded because of conversion to an

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Paper accepted 10 December 1995

Table 1 Clinical details and indications for surgery

	Patients given standard therapy (*n* = 40)	Patients given peritoneal injection (*n* = 40)
Median (range) age (years)	53 (22–80)	47 (20–79)
Sex (M:F)	16:24	14:26
Indication for surgery		
Biliary colic	3	4
Chronic cholecystitis	27	26
Acute cholecystitis	7	5
Acute pancreatitis	2	3
Empyema	1	2

Table 2 Pain level after laparoscopic cholecystectomy in patients given either standard therapy or peritoneal injection measured using a visual analogue pain scale (VAPS)

	VAPS of patients given		
	Standard therapy	Peritoneal injection	*P**
6 h after operation			
At rest	3·0 (2·4–4·1)	1·0 (1·1–2·3)	<0·01
On movement	5·0 (3·9–5·7)	2·9 (2·7–4·4)	<0·05
18 h after operation			
At rest	1·9 (1·5–3·0)	0·0 (0·3–0·8)	<0·01
On movement	3·2 (2·7–4·6)	1·2 (1·2–2·5)	<0·01

Values are median (interquartile range). *Mann–Whitney *U* test

Table 3 Analgesic requirement during and after laparoscopic cholecystectomy

	Patients given standard therapy	Patients given peritoneal injection
Intraoperative morphine (mg)	6	6
Postoperative pethidine (mg) per patient (i.m.)	36	23
Postoperative naproxen (mg) per patient (o)	116	127

Values are medians. Differences are not significant. Analgesia was supplied in 50-mg increments of intramuscular pethidine and 550-mg (×2) increments of naproxen sodium. i.m., Intramuscular; o, oral

open procedure after randomization (this was the result of difficulties in delineating the anatomy due to chronic cholecystitis in each patient). Patient details and indications for surgery were similar in each group (*Table 1*). The ASA grade was 1 in 68 per cent of patients who received standard technique *versus* 83 per cent in those who were given peritoneal injection. The remainder were grade 2. There were no major complications; minor intraoperative complications included peritoneal bile contamination (five standard technique *versus* three peritoneal injection), peritoneal blood contamination (none standard technique *versus* two peritoneal injection), peritoneal bile and blood contamination (three standard technique *versus* two peritoneal injection) and one gallbladder perforation in each group. The use of a 5-mm suction drain to the gallbladder bed was confined to ten patients given standard technique and eight who received peritoneal injection.

There was a significant reduction in the median VAPS in the study group at both 6 and 18 h after operation, both at rest and on movement (*Table 2*) in patients who had peritoneal bupivacaine. The median intraoperative analgesia given was identical in each group at 6 mg morphine (*Table 3*). Median postoperative intramuscular opiate and oral analgesic requirements were also similar in both groups.

Discussion

This study has confirmed a clinical impression that direct periportal injection of bupivacaine, at the level of the parietal peritoneum, reduces postoperative pain. This technique adds 2–3 min to the overall procedure and is easy to learn. It is performed under direct vision and is therefore safe. The benefits of good control of immediate postoperative pain, allowing swift mobilization, continue well past the time that the effect of the local anaesthetic is likely to have worn off[5]. The significant discomfort found in the control group is similar to that noted in a previous study from the authors' department when only pain scores at rest were obtained[3]. Other studies have reported significant pain in the first 48 h after laparoscopic cholecystectomy[4,6].

The use of intraperitoneal local anaesthetic at laparoscopy is not new, although to the authors' knowledge direct infiltration into the peritoneum around the port entry sites has not been performed before. Diagnostic laparoscopy is a common outpatient procedure, particularly for gynaecological complaints, and shoulder-tip pain is reported in as many as 35–63 per cent of cases afterwards[7]. The aetiology of shoulder-tip pain is presumed to be a residual pocket of subdiaphragmatic gas above the right lobe of liver. Using a visual analogue scale, Narchi *et al.*[8] found intraperitoneal infiltration of local anaesthetic into the right subdiaphragmatic area to reduce postoperative scapular pain after diagnostic laparoscopy.

Rademaker and colleagues[9] investigated the potential analgesic effect of bupivacaine instillation into the right subdiaphragmatic area in patients undergoing laparoscopic cholecystectomy. Although no benefit was reported, the precise localization of the pain was not specified and it is the authors' experience that patients undergoing laparoscopic cholecystectomy rarely suffer from postoperative shoulder-tip pain, although up to 80 per cent of patients may be affected in the first 24 h after gynaecological laparoscopy[10]. In one study, 55 per cent of patients also complained of abdominal pain some 48 h after gynaecological laparoscopy[10]. The difference in incidence of shoulder-tip pain may be positional. Laparoscopic cholecystectomy is generally performed in a slight reverse Trendelenburg position, the opposite of laparoscopic pelvic surgery. During laparoscopic cholecystectomy any spilled blood or bile collects in the paracolic gutter and supracolic compartment. It is routine to suction this area precisely, thus also evacuating any gas pocket.

Narchi *et al.*[11] performed peritoneal biopsy 2–3 days after laparoscopy and demonstrated peritoneal inflammation resulting from capillaries torn at the time of abdominal distension. Gillberg and colleagues[12] investigated 46 women who had gynaecological laparoscopy and found postoperative pain to be significantly reduced when a non-steroidal anti-inflammatory drug was given before anaesthesia. Pain resulting from stretching the whole parietal peritoneum should be less specific and more generalized than that found in previous studies. The total dose of bupivacaine was limited to 20 ml of 0·5 per cent for each patient, less than that used safely by Narchi *et al.*[8], to avoid potential toxicity. In addition, by raising an intraperitoneal bleb, the effect is likely to be a slower release into the circulation than in the case of direct instillation. Bupivacaine was diluted with 20 ml sterile water in the treatment group, to give the same total volume of anaesthetic subcutaneously to patients in both groups, although this meant that patients in the study group (peritoneal injection) had a reduced concentration of subcutaneous local anaesthetic injected.

This technique of periportal bupivacaine injection is simple, quick and reduces immediate postoperative pain after laparoscopic cholecystectomy.

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British Journal of Surgery 1996, **83**, 1226–1229

Cost–utility analysis of home parenteral nutrition

D. M. RICHARDS and M. H. IRVING

University of Manchester Intestinal Failure Unit, Hope Hospital, Salford M6 8HD, UK
Correspondence to: Mr D. M. Richards

An economic evaluation of home parenteral nutrition (HPN) for intestinal failure is presented. The cost–utility of HPN and factors affecting the cost–utility ratio were examined to determine whether current practice is the most efficient way of treating intestinal failure. Quality-adjusted life-years (QALYs) gained were measured using a validated health status questionnaire. The cost of treating a patient with intestinal failure was calculated, and marginal cost per QALY gained ratios were obtained. The cost per QALY for an average patient was approximately £68 975, but the value for patients over 55 years of age of about £126 865 compared with approximately £58 233 for those under 44 years. Treating a patient in hospital rather than at home increased the estimated cost per QALY to approximately £190 000. The current practice of home care is about 65 per cent more cost-effective than hospital care.

Home parenteral nutrition (HPN) is a life-saving but expensive treatment for intestinal failure. Intestinal failure is defined as the failure of intestinal function to provide sufficient nutrients and fluids to meet metabolic requirements. Patients with intestinal failure would be subjected to a combination of dehydration and malnutrition without HPN, and there would be an almost inevitable progression to death[1].

The treatment involves the administration of nutrient solutions through a long-term central venous catheter. HPN is complex and time-consuming for the patient and involves an average of 2–3 weeks of training[2].

In the face of budget constraints and increasing demands on healthcare, it is important that all healthcare interventions demonstrate cost-effectiveness when compared with alternative treatments and other healthcare programmes. This need is reflected in the current National Health Service (NHS) Research and Development Strategy and in particular the Health Technology Assessment Programme, in which evidence of effectiveness, quality-of-life assessment and economic appraisal has a high priority. In addition, following the purchaser–provider split within the NHS, cost-effectiveness data will play an integral part in contract setting.

As with similar technologies, HPN programmes are competing for increasingly scarce resources, and there is an urgent need for this type of assessment. To date, the authors are not aware of any economic appraisal of HPN from the UK.

Cost–utility analysis is an economic tool for assessing healthcare programmes and is useful for comparing different treatments for the same condition (assessing operational efficiency) or different technologies across the healthcare spectrum (assessing allocative efficiency). It evaluates outcomes in terms of utility, which is used as a measure of satisfaction. The most common method of representing utility is the quality-adjusted life-year (QALY). QALYs are the units of measurement resulting from the product of data on survival and quality of life[3], and are the measurement of outcome used in a cost–utility analysis. It is important to calculate the resources consumed by a technology and convert these into a monetary equivalent. The marginal cost, the cost to treat one additional patient, is the most useful measure of resource consumption. The costs are combined with the outcome (QALYs gained) to give a ratio of cost–utility. Different technologies can then be compared on a marginal cost per QALY gained basis.

Cost–utility analysis has been used in this setting for two main reasons. First, it gives an indication of the quality of the life-years gained, an important factor for patients receiving HPN. Second, the main concern is with allocative efficiency, determining whether HPN treatment is worthwhile compared with other healthcare programmes. If other treatments were available for intestinal failure then they could be compared on a cost–utility basis, but as there are no viable alternatives at present HPN has been compared with the alternative of no treatment.

Patients and methods

Objectives

The study was designed to measure the cost–utility of HPN, to examine factors affecting the cost–utility ratio and to determine whether current practice is the most cost-effective way of treating patients with intestinal failure.

The alternatives

Patients are trained in hospital for approximately 3 weeks and then discharged. They look after the central-line and carry out the complex procedure of fluid administration. Admissions to hospital are restricted to times when complications arise; these are usually central-line or metabolic derangements. There are no viable alternatives that can be considered at the present time, apart from keeping patients with intestinal failure in hospital or admitting them for intermittent therapy. This policy has been shown to be less cost-effective[4], and almost impossible for the present cohort of patients, as they lived an average of 85 miles from the unit and fed for a median of 6 nights per week. Small bowel transplantation is a developing future option[5], but owing to problems with immunosuppression it is not widely available[6]. HPN would still be required while donor organs were awaited.

Perspective

This study has been performed from the broad perspective of the NHS. It includes costs relevant to the NHS but does not explore the cost to individual patients, such as change in employment status, travel costs and time.

Paper accepted 23 November 1995

Patients

There are three main centres providing HPN services in the UK: Hope Hospital in Salford, St Mark's Hospital in London and Dundee Royal Infirmary. However, because there are a further 47 centres with only a handful of patients each, there will be inevitable variation in practice throughout the country. The results from different centres will vary according to the experience of the centre[7]. The resources used will be subject to variation due to local factors affecting costs; in particular, the cost of the parenteral solutions will vary according to the supplier It was decided, on the basis of variation in practice and costs, that the authors should concentrate on patients curently monitored by Hope Hospital. The explicit presentation of the results meant that local factors could be taken into account, and 'centre-specific' QALY values calculated.

Hope Hospital monitors the largest group of patients receiving HPN in the UK ($n = 64$, June 1995), equivalent to approximately 35 per cent of the total UK population of patients having HPN[8]. There is extensive information on survival and morbidity rates[2]. The patients were treated according to standard protocols and monitored by a multidisciplinary nutrition team. The mean age was 44·4 (range 17–70) years, and 40 were women. All patients were suffering from intestinal failure, the commonest diagnosis being Crohn's disease ($n = 35$, 55 per cent) followed by mesenteric vessel occlusion ($n = 11$, 17 per cent) and volvulus ($n = 8$, 12 per cent). The remaining ten patients had a variety of diagnoses. None of the patients had acquired immune deficiency syndrome (AIDS) or active cancer. All had received at least 6 months of nutrition at home. The median duration of HPN treatment was 4 (range 0·5–15) years, HPN being infused on a cyclical nocturnal basis in 63 patients for a median of 6 (range 2–7) nights per week.

Methodology

The utility scores were obtained using the EuroQol Health Status Questionnaire[9]. This validated subjective instrument yields an index on a scale of 0 to 1. A score of 1 would be the best possible quality of life, while 0 would be equivalent to death. A range of survival times was considered because of uncertainty regarding survival outcomes. This methodology was used by Gudex[10] when dealing with the same problem.

The number of QALYs gained was calculated by multiplying length of survival by the quality-of-life index. They were discounted at the rate published by the UK Treasury (6 per cent per annum). Non-discounted values are also presented, reflecting the view that there is no time preference for health outcomes. The QALYs gained are calculated assuming that life is not possible for patients with intestinal failure without HPN[1].

The marginal costs (the cost to treat one additional case of intestinal failure) were calculated assuming that there was some spare capacity in the unit and that no additional buildings or staff were required. The determination of marginal costs was carried out in three phases, according to the methodology described by Drummond[11]: (1) enumeration of the resources used, i.e. a list of all the resources thought to be relevant (*Appendix 1*); (2) measurement of resource use, i.e. the actual number of resources consumed; and (3) the explicit valuation of resources, valuing the resource consumption in terms of money (future costs discounted at 6 per cent).

Cost–utility ratios were calculated for a range of survival times. A sensitivity analysis was performed to examine the factors affecting the cost–utility ratios. The factors explored were age, hospital admission and length of survival without HPN.

Results

The mean utility score derived from the EuroQol instrument for patients with HPN was 0·52. The score was 0·61 for patients under 44 years and 0·28 for older patients.

The costs for the first year are given in *Table 1*. Subsequent years will not include the cost of a pump, trolley, drip stand, fridge and hospital training; therefore the costs for the second year onwards (non-discounted) were £36 848. The incremental discounted costs for each year of survival are shown in *Table 2*. The total discounted cost for (median) 4 years of treatment is £142 089. If a patient is treated as an inpatient for the 4 years then the discounted cost increases to £312 595. The potential savings for home rather than hospital HPN for the median duration of 4 years are £170 506.

The number of QALYs gained for each year of survival is shown in *Table 2*. It will be some years before the survival of the present group of patients is known, and cost–utility ratios are therefore presented for a range of survival times in *Table 2*. The marginal cost per QALY gained for a patient surviving for 4 years is £68 975. If longer survival is experienced, then the marginal cost per QALY falls.

Sensitivity analysis

The utility score for a patient who manages to survive without HPN has been estimated at 0·18[4]. This figure would mean that the QALY gain would be reduced to only 0·34 for a patient with HPN surviving 1 year, and the cost per QALY would then increase from £85 829 to £130 259. If the discount rate is reduced to 0 per cent, the cost per QALY for a patient surviving 4 years would be

Table 1 Costs to the National Health Service for year 1

	Cost (£)
In-hospital stay for training and line insertion (including all staff, hotel and investigation charges for 3 weeks)	4513
In-hospital TPN and disposable charges	1428
Outpatient monitoring (four visits)	600
Pump, trolley, fridge and drip stand	3590
Home TPN for 6 nights per week (median) (using a home-care company supplying disposables for 49 weeks)	34157
Total	44288

TPN, total parenteral nutrition

Table 2 Quality-adjusted life-years gained, incremental costs and marginal costs per quality-adjusted life-year gained for a range of survival times

Years survived	QALYs gained	Discounted incremental cost (£)	Marginal costs per QALY gained (£)
1	0·516	44288	85829
2	1·03 (0·97)	78925	76626
3	1·55 (1·29)	111484	71925
4	2·06 (1·61)	142089	68975
5	2·58 (1·89)	170857	66224
6	3·10 (2·14)	196277	63315
7	3·60 (2·34)	220172	61159
8	4·12 (2·52)	242633	58891
9	4·64 (2·66)	263747	56842
10	5·16 (2·78)	283594	54734

Values in parentheses are the number of quality-adjusted life-years (QALYs) gained discounted at 6 per cent

£75 161. At a 10 per cent discount rate this value would fall to £65 126. The present patients were not kept in hospital for long-term HPN but the effect can be estimated. The utility fell by 20 per cent when Torrance *et al.*[12] measured the difference between home and hospital renal dialysis. If the same fall is assumed when patients with HPN are kept in hospital, then a patient treated in hospital for the median 4 years would gain only 1·65 QALYs. The discounted hospital costs for this period are £312 595 and the cost per QALY is therefore £189 451.

Younger patients had higher utility scores (0·61), and this reduces the cost per QALY to £58 233. For older patients the cost per QALY rises to £126 865 because of the lower utility (0·28). One of the commonest complications of HPN is central-line sepsis. Two episodes of line sepsis (in years 2 and 4), which required attempted salvage and replacement of the central line, led to a discounted direct cost of £3660. This sum increases the cost per QALY over 4 years to £70 751.

Discussion

Economic appraisals of HPN have rarely been performed, particularly in the UK. This fact is surprising considering the costs associated with HPN programmes. Wateska *et al.*[13] analysed costs of HPN compared with those of hospital total parenteral nutrition (TPN) and noted a cost reduction of 73 per cent for HPN. Other cost analyses have also demonstrated that HPN is 72–81 per cent cheaper than hospital treatment[14 15]. Baptista and co-workers[16] suggested regular reassessment for compliance, appropriateness of formulation, infusion regimen, bowel adaptation and oral intake so that optimum cost-effective care can be provided for an individual.

Detsky *et al.*[4] performed a cost–utility analysis of HPN in Toronto, which was based on utility scores measured in 37 patients and estimated for a further 36. Detsky[17] has admitted that the scores they obtained were higher than those expected (0·7 on a scale of 0 to 1). This study measured the net savings in healthcare costs as $19 232 (1986 Canadian) per patient. The cost per QALY was estimated to be $27 375 (1986 Canadian).

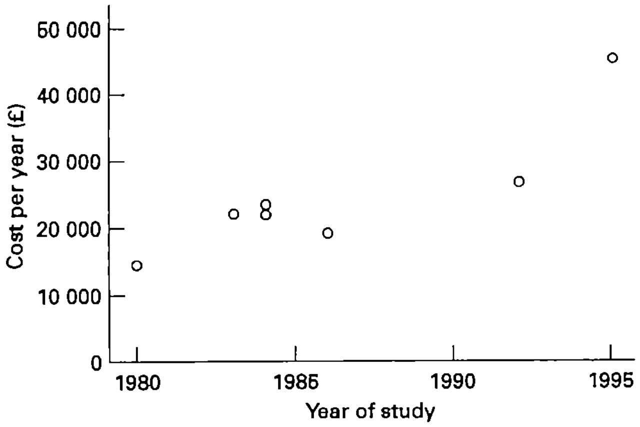

Fig. 1 Annual cost of home parenteral nutrition cited by different authors (from left to right, References 13–16, 4, 18 and the present paper respectively)

Unfortunately, there are few alternatives to HPN. At present the only possible alternative to home treatment is keeping the patient in hospital, or admission for intermittent therapy. Small bowel transplantation is not yet considered a routine procedure, although there are hopes that one day it may replace the need for long-term HPN[6]. Patients waiting for a small bowel transplant would still need HPN during the period of observation necessary to assess the degree of adaptation.

This study has confirmed that HPN is an expensive technology. The costs are escalating in excess of inflation (*Fig. 1*). However, HPN is life-saving for many patients. The quality-adjusted survival for younger patients (under 44 years) is significantly better than that for older (over 55 years) patients, and this fact significantly reduces the marginal cost per QALY. The longer a patient survives on HPN the more cost-effective the treatment becomes. Weaning from HPN due to intestinal adaptation reduces the cost per QALY even further.

Detsky *et al.*[4] estimated the increase in quality-adjusted survival as 3·3 years, compared with the alternative of treating the patient in hospital. Messing and co-workers[19] measured the survival of a cohort of 217 patients. No patients were lost to follow-up, and the probability of survival for benign conditions at 5 years was 62 per cent. In the USA and Italy malignant disease is the commonest indication for HPN, and AIDS is an increasing indication. There were no patients with AIDS or terminal malignant disease in the present study, but if they were included the survival rate would drop sharply and consequently the cost per QALY would rise steeply.

This study has shown that HPN is more cost-effective than hospital care. The estimated savings for each patient (on TPN for 4 years) treated at home rather than in hospital are £170 506. The cost per QALY for hospital care was almost £190 000 and £68 975 for HPN. This figure means that the cost–effectiveness of home care is approximately 65 per cent greater.

The sensitivity analysis showed that the cost per QALY was sensitive to the possibility of survival without HPN. HPN is therefore most cost-effective when it is used as a life-saving technology. Although it is difficult to see how a patient could be kept as an inpatient for the duration of required therapy, this alternative had to be considered and the cost per QALY was found to be very high. Because of the fall in utility values associated with patients over the age of 55 years, the results were sensitive to age. Altering the discount rate or treating line sepsis during the course of HPN treatment did not significantly affect the results. It should be remembered that QALYs are not without their critics[20,21], but measuring and valuing the quality of life is an extremely difficult process.

League tables showing 'marginal cost per QALY gained' have been constructed to compare different healthcare interventions. When HPN treatment is compared with home haemodialysis, it appears that HPN is much less cost-effective (£69 000 per QALY compared with £23 500). However, intestinal function recovers in approximately 75 per cent of patients with Crohn's disease, and HPN becomes much more competitive on a cost-per-QALY basis because of the consequent increase in QALYs gained. There have been criticisms of cost-per-QALY tables because of the differing methodologies used and failure to use marginal costs[22]. Despite the criticisms, explicit presentation of cost-effectiveness is an improvement on the implicit decision-making process of the past. In Oregon, USA, different treatments have been competing for scarce resources with regard to the marginal cost per QALY gained[23].

In conclusion, HPN is an expensive technology with a reasonable outcome for younger patients with benign disease in terms of the number of QALYs gained. The cost-effectiveness of HPN is lower for older patients and those in hospital care. HPN is approximately 65 per cent more cost-effective than keeping patients in hospital. The expense of the treatment is offset by the life-saving nature of the technology.

Acknowledgements

Financial support for this work was obtained from the University of Manchester, UK. Invaluable training in health economics and advice was obtained from the Centre for Health Economics, University of York and from the Health Economics Research Unit, University of Aberdeen, UK.

Appendix 1

Resource utilization assessment

Duration on HPN	Median 4 years
No. of nights on TPN	Median 6 nights

Inpatient stay

Duration of inpatient training	Mean 21 days

Routine inpatient pathology tests

Full blood count (twice weekly). Urea and electrolytes (twice weekly). Prothrombin time (PT) and clotting screen (PTTK) (twice weekly). 24-h urine for urea and electrolytes (once weekly). Estimation of magnesium, copper, zinc, iron, C-reactive protein (CRP) and orosomucoids (once per month). One exit site swab per week.

Consumables

Dressing packs. Gloves. Giving sets. Alcohol wipes

Pharmacy costs of TPN

Electrolyte bag. Fat bag. Glucose bag. Trace elements. Vitamins. Heparin

Theatre time, average length of time for insertion. Radiographic screening. 20-min radiographer time. 2-min screening. 1 Broviac line.

Home equipment. Fridge. Pump. Drip stand. Trolley.

Consumable supplies. Annual totals for sterile supplies. Annual totals for electrolyte bags. Annual totals for nutrition. Outpatient monitoring clinic. Total no. of visits per year. Outpatient blood tests. Full blood count. Urea and electrolytes. Liver function tests. Bilirubin. Phosphates. Ferritin. Copper, magnesium, zinc, iron CRP and orosomucoids. PT, PTTK and erythrocyte sedimentation rate.

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British Journal of Surgery 1996, 83, 1230–1233

Randomized controlled trial of the effect of mannitol on renal reperfusion injury during aortic aneurysm surgery

M. L. NICHOLSON, D. M. BAKER, B. R. HOPKINSON and P. W. WENHAM

University Hospital, Nottingham, UK

Correspondence to: Mr M. L. Nicholson, Department of Surgery, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK

The effects of mannitol on renal impairment following infrarenal aortic aneurysm repair were studied. Patients received either mannitol 0·3 g/kg ($n = 15$) or saline ($n = 13$) as a rapid intravenous infusion before aortic cross-clamping. One patient in the control group developed fatal postoperative renal failure but there was no renal failure in the mannitol group. Two patients treated with mannitol died from perioperative myocardial infarction. There were no significant differences in postoperative blood urea level, serum creatinine concentration or creatinine clearance between mannitol and control groups. In patients who had mannitol there was a significant diuresis on the first day after operation (mean urine output 2250 ml) compared with before operation (1557 ml) ($P = 0·007$). Compared with controls, patients treated with mannitol had lower mean(s.e.m.) postoperative levels of urinary albumin (160(32) *versus* 500(140) mg per mmol creatinine; $P = 0·036$) and *N*-acetyl glucosaminidase (143(34) *versus* 271(70) μmol per mmol creatinine; $P = 0·04$) indicating a reduced level of subclinical glomerular and renal tubular damage. These data demonstrate that mannitol reduces subclinical renal injury following infrarenal aortic aneurysm repair.

Acute renal failure is a serious complication of both emergency and elective aortic aneurysm repair, and is associated with a high mortality rate[1]. The cause of postoperative renal dysfunction is likely to be multifactorial, but aortic cross-clamping, which is necessary during this surgery, is an important factor. Such clamping is associated with marked changes in renal haemodynamics and subsequent reperfusion injury, both of which adversely affect renal function[2,3]. The protective effect of mannitol in preventing ischaemic renal damage has been studied previously[4–6] and some surgeons use it routinely during aortic aneurysm surgery. In this study a controlled trial was designed to test the effects of mannitol on renal function and injury following aortic aneurysm repair.

Patients and methods

Twenty-eight consecutive patients undergoing elective aortic aneurysm repair were entered into a prospective randomized trial. All operations were performed under general anaesthesia with the patients paralysed and mechanically ventilated. An epidural catheter was placed before operation, unless contraindicated, and the anaesthetic agents used were fentanyl, etomidate, isoflurane and nitrous oxide in oxygen. A urinary catheter was placed in all patients after the induction of anaesthesia. Patients were then randomly allocated to receive either mannitol 0·3 g/kg or an equivalent volume of normal saline given as a rapid intravenous infusion before cross-clamping the aorta. Randomization was by means of opening a sealed envelope following the induction of anaesthesia. The sealed envelopes were generated using a table of random numbers. All operations were performed by, or under the direct supervision of, two consultant surgeons (P.W.W. and B.R.H.). After administration of systemic heparin 3000–5000 units, the infrarenal aorta and iliac arteries were clamped. The aneurysm sac was then opened and replaced with either a straight or bifurcated Dacron graft (Du Pont, Stevenage, UK), depending on the distribution of the aneurysmal disease.

Assessment of renal function and injury

Renal function was assessed after operation by measuring urine output, creatinine clearance, and blood urea and serum creatinine levels. Renal failure was defined as urine output below 400 ml per 24 h and/or the need for dialysis. Venous blood was drawn for urea and electrolyte estimation before operation and then at 6 h, 24 h, 3 days and 7 days after surgery. Glomerular filtration rate was estimated by performing 24-h creatinine clearances before operation and then on the first, third and seventh days after operation. Aliquots of urine (10 ml) were collected at the following times: before surgery, after induction of anaesthesia but before mannitol or saline infusion and cross-clamping, 60 min after cross-clamp release, and 6 h, 24 h and 7 days after surgery. These aliquots were stored at −70°C for subsequent batch analysis of urinary albumin, *N*-acetyl glucosaminidase (NAG) and creatinine. Results were expressed as albumin : creatinine and NAG : creatinine ratio.

Statistical analysis

Data are presented as mean(s.e.m.) or 95 per cent confidence interval (c.i.). Discrete variables were compared using Fisher's exact test. Continuous variables were compared using the Mann–Whitney *U* test (for differences between mannitol and control groups), and the Wilcoxon signed rank test (for changes within groups). Statistical significance was accepted at $P < 0·05$.

Results

Patients in the mannitol and control groups were well matched for age, sex and preoperative risk factors (*Table 1*). Operative details are shown in *Table 2*. Aortic cross-clamp time ranged from 29 to 110 (mean 57) min in the mannitol group and from 27 to 102 (mean 53) min in the control group ($P = 0·76$). There were no significant differences between groups for total anaesthetic time and the duration of intraoperative hypotension below 80 mmHg systolic pressure (*Table 2*).

Clinical outcome

Mean(s.e.m.) postoperative stay in the intensive therapy unit was 2·1(0·4) days in the mannitol group and 1·5(0·2)

Paper accepted 14 December 1995

Table 1 Patient characteristics

	Mannitol ($n = 15$)	Control ($n = 13$)
Mean age (years)	68 (65–72)	71 (68–75)
Sex (M:F)	13:2	11:2
Ischaemic heart disease	6	4
Smokers	13	11
Hypertension	5	6
Chronic obstructive airway disease	1	2
Thromboembolic disease	0	1
Diabetes	0	1

Values in parentheses are 95 per cent confidence intervals. There was no significant difference between groups

Table 2 Operative data

	Mannitol ($n = 15$)	Control ($n = 13$)
Graft type		
Straight	11	9
Bifurcated	4	4
Total anaesthetic time (min)	162 (147–177)	175 (159–191)
Duration of intraoperative hypotension (< 80 mmHg) (min)	21 (8–34)	27 (17–37)
Aortic cross-clamp time (min)	57 (43–71)	53 (39–68)
Peroperative blood transfusion (units)	2·6 (1·5–3·7)	2·7 (1·2–4·2)

Values are mean (95 per cent confidence intervals). There was no significant difference between groups

Table 3 Postoperative complications and deaths

Complication	Mannitol	Control
Death	2	1
Renal failure	0	1
Myocardial infarction	2	0
Respiratory failure	1	1
Left ventricular failure	1	0
Atrial fibrillation	1	0
Chest infection	1	2
Trash foot	1	2
Wound dehiscence	0	1
Diarrhoea	2	0

There was no significant difference between groups (Fisher's exact test)

days in the control group ($P = 0·43$). Mean(s.e.m.) total inpatient stay was 10·6(0·4) days in patients who had mannitol and 10·3(0·6) days in controls ($P = 0·62$). Postoperative complications and deaths are shown in *Table 3*. Ten of 15 patients in the mannitol group and six of 13 in the control group suffered one or more postoperative complications. Both deaths in the mannitol group resulted from perioperative myocardial infarction in patients with known ischaemic heart disease and hypertension. There was no postoperative renal failure in the mannitol group. In the control group the single death was a result of multiple organ failure including adult respiratory distress syndrome, acute renal failure and bilateral trash foot. There were no statistical differences between the rates of other major postoperative complications between the two groups (*Table 3*).

Renal function

Changes in levels of blood urea, serum creatinine and creatinine clearance are shown in *Table 4*. There were no significant differences in these three measures of renal function between patients receiving mannitol and controls, and comparing results within each group against time. Perioperative 24-h urine output is shown in *Fig. 1*. In the

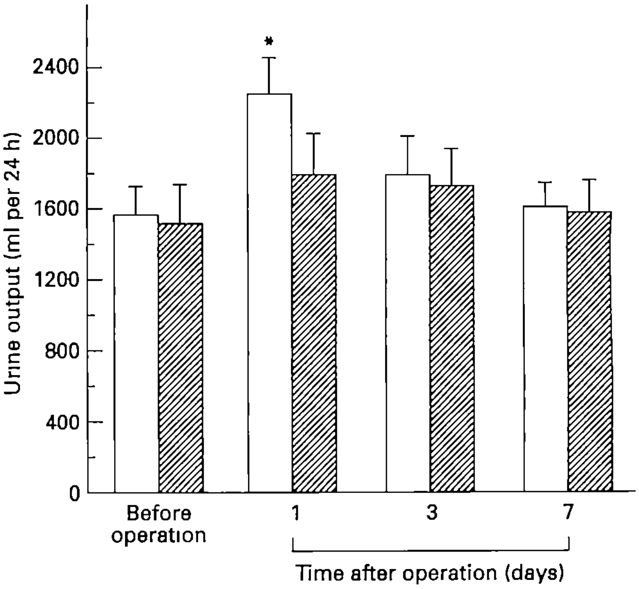

Fig. 1 Mean urine output in patients receiving mannitol (□) or saline (▨) before aortic aneurysm repair. Bars represent s.e.m. *$P < 0·01$ *versus* before operation

Table 4 Perioperative renal function in aortic aneurysm repair

	Blood urea (mmol/l)		Serum creatinine (μmol/l)		Creatinine clearance (ml/min)	
	Control	Mannitol	Control	Mannitol	Control	Mannitol
Before operation	7·1(1·2)	5·9(0·4)	120(8)	107(6)	63·2(6·6)	61·5(6·2)
After operation						
6 h	6·6(0·9)	6·1(0·4)	119(11)	111(11)	—	—
24 h	8·3(1·1)	6·6(0·6)	136(19)	105(9)	63·6(10·2)	57·6(10·7)
3 days	7·6(1·1)	6·8(0·8)	125(14)	104(7)	67·7(10·1)	68·7(9·1)
7 days	7·2(0·8)	5·8(0·8)	111(9)	103(7)	64·6(9·9)	70·9(7·0)

Values are mean(s.e.m.)

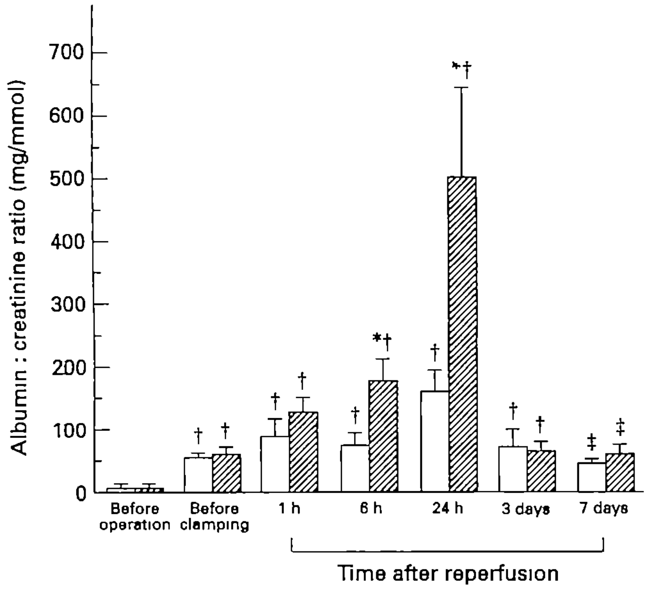

Fig. 2 Mean urinary albumin:creatinine ratio in patients receiving mannitol (□) or saline (▨) before aortic aneurysm repair Bars represent s.e.m. *$P<0\cdot05$ *versus* patients given mannitol; †$P<0\cdot001$, ‡$P<0\cdot01$ *versus* before operation

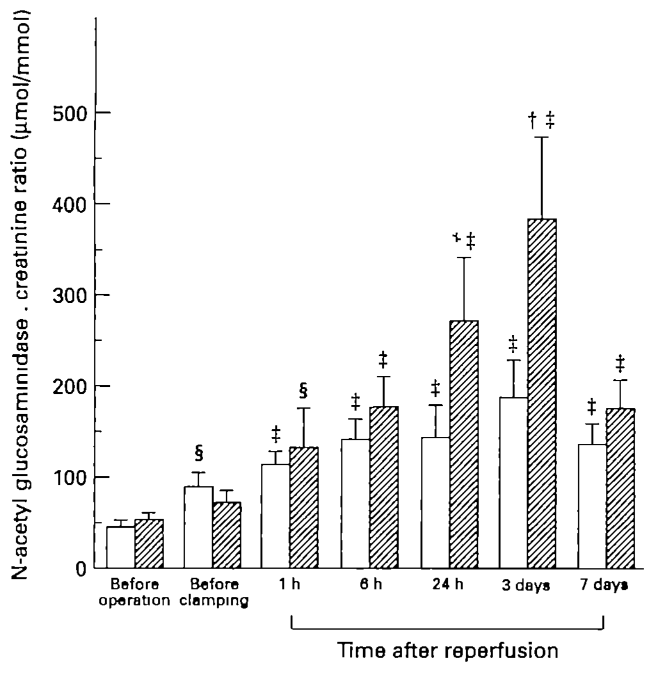

Fig. 3 Mean urinary *N*-acetyl glucosaminidase·creatinine ratio in patients receiving mannitol (□) or saline (▨) before aortic aneurysm repair. Bars represent s e m *$P<0\cdot05$, †$P=0\cdot06$ *versus* patients given mannitol; ‡$P<0\cdot01$, §$P<0\cdot05$ *versus* before operation

mannitol group there was significant diuresis on the first day after surgery compared with before operation. Although urine output over the first day after operation was higher in patients who had mannitol than in controls, the difference was not significant.

Renal injury

Urinary albumin:creatinine and NAG:creatinine ratios are shown in *Figs 2* and *3* respectively. In both mannitol and control groups the ratio of urinary albumin to creatinine increased from the preoperative level to a peak at 24 h after operation and then declined. The albumin:creatinine ratio increased significantly after the induction of anaesthesia but before aortic clamping; it did not decline to the baseline preoperative level by the seventh day after operation. The urinary albumin:creatinine ratio was significantly higher in controls compared with those receiving mannitol at 6 h after reperfusion ($P=0\cdot027$) and at 24 h after reperfusion ($P=0\cdot036$). Urinary NAG:creatinine ratio also increased following anaesthesia and reperfusion, reaching a peak on the third day after operation and then falling by the seventh day. The increase was smaller in the mannitol group than in controls and the NAG:creatinine ratio was significantly higher in control patients than in those given mannitol at 24 h after reperfusion ($P=0\cdot04$). Urinary NAG:creatinine ratio increased after the induction of anaesthesia but before aortic cross-clamping in both mannitol and control groups ($P<0\cdot01$) and had not returned to the baseline preoperative level by the seventh day after surgery ($P<0\cdot01$).

Discussion

Biochemical tests of renal function are relatively insensitive as large changes in function must occur before such biochemical measurements alter significantly. For example, serum creatinine only rises above the upper limit of the reference range when over half the functional mass of renal tissue is lost[7]. It is, therefore, not surprising that there were no significant differences in perioperative renal function between the mannitol and control groups. Similarly, renal failure cannot be used as an endpoint in human studies because the incidence following elective aortic aneurysm is relatively low and a very large number of patients would be needed to demonstrate a difference between therapies. For these reasons, renal injury was also assessed by measurement of urinary albumin and NAG excretion. Albuminuria is known to be an accurate index of renal glomerular damage[8]. Urinary albumin excretion has been shown to rise rapidly during aortic surgery, and appears to be a useful measure of reperfusion injury and a predictor of the development of postoperative pulmonary complications[9]. NAG is one of over 30 enzymes found in the urine. It is predominantly a proximal tubular cell lysozymal enzyme and its excretion provides an early indicator of renal tubular damage[10]. Urinary NAG measurement is a sensitive index of subclinical renal impairment in obstructive jaundice[11]. To take account of differing urinary flow rates and to correct for differences in dilution, the urinary excretion of albumin and NAG were expressed as ratios to urinary creatinine clearance. These two indices provide a sensitive assessment of subclinical renal damage and allow a useful comparison between groups in a situation where there are no apparent clinical differences.

The data show that there is subclinical renal impairment during elective aortic aneurysm repair and that mannitol has a protective effect on this. The only instance of postoperative renal failure developed in a patient in the control group and this proved to be fatal. This study may contain a type II statistical error and it may be possible to demonstrate a clinically significant effect of mannitol if larger numbers of patients are studied. Although it is probable that clinical rather than subclinical renal impairment is more likely to occur in cases of ruptured abdominal aortic aneurysm, this is a much more difficult situation in which to conduct a clinical study.

The mechanism of renal injury following aortic aneurysm repair has been the subject of much debate. In particular, the effects of aortic cross-clamping have been controversial, and the extensive experimental and clinical literature on this subject has been well discussed recently by Welch *et al.*[12]. Infrarenal cross-clamping of the abdominal aorta causes a marked increase in systemic resistance above the clamp, with a 75 per cent increase in renal vascular resistance and a 38 per cent decrease in renal blood flow[2]. In addition, a fall in glomerular filtration rate follows release of the aortic cross-clamp; this can be delayed but not prevented by dopamine[13]. Other mechanisms may also be involved, such as microembolism of the renal vascular bed[14] and stimulation of the renin–angiotensin system[15].

Release of the aortic clamp may be just as important as the changes in renal haemodynamics occurring during cross-clamping. Sudden re-establishment of the circulation to the lower torso and legs causes generation of oxygen-derived free radicals, followed by formation of thromboxane A_2 and activation of neutrophils[16]. Oxygen free radicals and activated neutrophils cause both local and distant tissue damage in a number of organs. For example, reperfusion following aortic aneurysm repair causes pulmonary injury[17]. As a highly oxygenated organ, the kidney is especially vulnerable to attack from the oxygen free radicals of reperfusion[3].

Mannitol has a number of actions which may protect renal function during aortic surgery. Its osmotic diuretic action has been confirmed in the present study in which early postoperative urine output was significantly increased in patients given mannitol. A good urine flow is thought to reduce renal impairment by preventing the precipitation of casts in the renal tubules, but the osmotic effect of mannitol in the renal tubules may also prevent endothelial cell swelling[18]. Mannitol also has beneficial effects on renal haemodynamics and has been shown to increase renal blood flow[19]. Finally, it is a powerful scavenger of the highly injurious hydroxyl radical which is a key mediator in reperfusion injury[3,20]. In this context, mannitol has been shown to attenuate skeletal muscle reperfusion injury in animal models[21] and pulmonary reperfusion injury following infrarenal aortic aneurysm repair in humans[22]. Neither renal haemodynamics nor oxidative stress were directly measured during this study and it is impossible to speculate further on the mechanism of action of mannitol.

In conclusion, this study demonstrates that mannitol has a protective effect against renal injury during infrarenal abdominal aortic aneurysm repair. It is a simple and inexpensive treatment without adverse effects. Further studies are required to evaluate the mechanism of action of mannitol, be it haemodynamic, free radical scavenging, or a combination of both.

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British Journal of Surgery 1996, 83, 1234–1237

Colour-coded duplex assessment alone before carotid endarterectomy

J. GOLLEDGE, R. WRIGHT, N. PUGH and I. F. LANE

Cardiff Vascular Unit, University Hospital of Wales, Cardiff, UK
Correspondence to: Mr J. Golledge, 35 Sullivans Reach, Walton on Thames, Surrey KT12 2QB, UK

This study assessed whether carotid colour-coded duplex imaging can provide sufficient information to investigate patients before carotid endarterectomy. One hundred patients with symptomatic carotid artery disease (amaurosis fugax 24, transient ischaemic attack 38 and established stroke 38) were assessed by both colour-coded duplex imaging and arch angiography. Stenoses were graded at angiography using the linear method from the European Carotid Surgery Trial and on duplex using peak systolic velocity criteria. Angiograms were also analysed for any arch or intracerebral pathology which would alter surgical management. In defining 70–99 per cent stenoses, duplex had a sensitivity of 98 per cent, specificity 96 per cent, positive predictive value 96 per cent, negative predictive value 98 per cent and accuracy 97 per cent compared with angiography for both symptomatic and asymptomatic carotids ($\chi^2 = 1{\cdot}22$, 1 d.f., $P = 0{\cdot}25$). With respect to the symptomatic carotid arteries angiography gave different information from duplex in six patients (6 per cent): definition of 70–99 per cent carotid stenosis was different (four), visualization was poor on duplex (one) and an intracerebral aneurysm was identified by angiography. One patient died following arch angiography as a result of mesenteric thrombosis. Carotid duplex imaging alone would appear to be sufficient to assess most patients before carotid endarterectomy as an accurate, safe and relatively cheap investigation compared with angiography. In cases where duplex assessment does not allow full visualization of the carotid bifurcation angiography is required.

North American[1] and European[2] carotid trials have clearly validated carotid endarterectomy as the optimal treatment for 70–99 per cent internal carotid artery stenoses[3]. Colour-coded duplex imaging technology has improved over the past 5 years, making it possible to visualize the carotid bifurcation and extracranial internal carotid artery without resort to angiography[4]. In a small number of vascular units, patients undergo carotid endarterectomy on the basis of duplex findings alone[4,5]. However, angiography provides visualization of the aortic arch, distal carotid arteries and intracerebral circulation, information not available from duplex.

The principal diagnostic guidelines in the management of carotid artery disease have been based on angiographic criteria[1,2] and it has been the practice in this unit to obtain carotid angiograms on all patients being considered for endarterectomy. This study compares the findings of angiography with those of duplex imaging in 100 consecutive patients with carotid artery disease and assesses the influence of angiography on surgical management.

Patients and methods

Between July 1992 and December 1994, 100 consecutive symptomatic patients (amaurosis fugax 24, transient ischaemic attack 38 and established stroke 38) had colour-coded duplex imaging (Toshiba FFH 140A and 270A, 5–7.5-MHz probes) and arch angiography (selective carotid injection, digital subtraction and two projections). Criteria for performing angiography were history of a focal cerebral event related to the carotid artery and duplex evidence of a tight stenosis or ulcerated plaque. Duplex scans were only repeated on admission for angiography if there was a delay between clinic assessment and angiography. There was a median delay of 3 (range 0–12) weeks between duplex imaging and angiography.

Median age of the 100 patients was 66 (range 42–84) years and 71 were men. Atherosclerotic risk factors included ischaemic heart disease (24 patients), hypertension (48), hyperlipidaemia (15), smoking (64) and diabetes mellitus (seven). At presentation, the majority of patients were taking aspirin (78), and a small number were receiving warfarin (three) or dipyridamole (two).

The degree of internal carotid artery stenosis was defined on duplex using peak systolic velocity at the site of maximal stenosis in addition to anatomical information from colour-coded B mode ultrasonography[6]. Angiographic degree of stenosis was estimated by measuring the degree of reduction of luminal diameter at the site of maximal stenosis, having assessed both projections, as in the European Carotid Surgery Trial[2] (*Fig. 1*). For the purpose of comparison, internal carotid disease was divided into less than 30 per cent, 30–69 per cent, 70–99 per cent or occlusion. Angiograms were also assessed for evidence of arch or intracerebral disease which would affect clinical management

Results

Colour-coded duplex imaging of the symptomatic carotid artery revealed internal carotid artery stenosis of less than 70 per cent in five patients, greater than 70 per cent in 90 and occlusion in four. In one patient it was difficult to establish the degree of internal carotid stenosis because of a heavily calcified plaque at the carotid bifurcation.

Comparison of colour-coded duplex imaging and angiography (Table 1)

Angiography confirmed duplex definition of degree of internal carotid stenosis in 95 symptomatic carotid arteries (stenosis 30–69 per cent, three; stenosis 70–99 per cent, 88; occlusion, four). In one patient duplex failed to image the origin of the internal carotid artery, while angiography showed diffuse internal carotid disease, and in four patients there was a significant variation in the degree of stenosis measured by the two techniques (*Table 2*). In

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Presented to The Vascular Surgery Society of Great Britain and Ireland, in London, UK, November 1995
Paper accepted 7 December 1995

one patient angiography demonstrated an anterior communicating artery aneurysm; no significant arch lesions were identified.

Specifically with respect to differentiating 70–99 per cent stenosis from less than 70 per cent stenosis or occlusion in both symptomatic and asymptomatic carotid arteries, duplex had a sensitivity of 98 per cent, specificity 96 per cent, positive predictive value 96 per cent, negative predictive value 98 per cent and an accuracy of 97 per cent compared with an angiographic standard. There was no significant difference in the findings of duplex and angiography in these groups ($\chi^2 = 1{\cdot}22$, 1 d.f., $P = 0{\cdot}25$, McNemar's test with continuity correction).

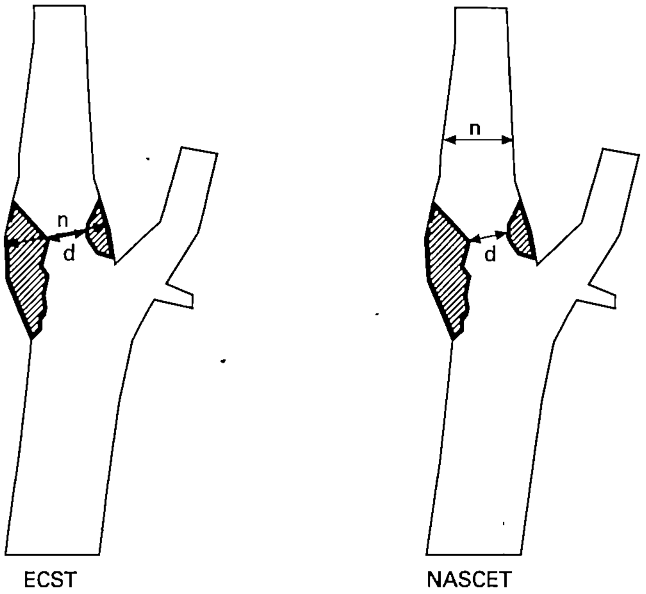

Fig. 1 Angiographic measurement of degree of internal carotid stenosis used in the European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET). In ECST (and this study) the residual lumen (d) was compared with the expected normal lumen at that site (n). In NASCET the residual lumen (d) was compared with the diameter of the distal normal internal carotid artery above (n). Percentage stenosis was calculated as 1 – d/n × 100

Table 1 Comparison of angiographic and colour-flow duplex definition of carotid stenoses

Stenosis (%) on duplex	Stenosis (%) on angiography			
	0–29	30–69	70–99	100
0–29	47	5	0	0
30–69	1	18	2	0
70–99	0	2	103	2
100	0	0	0	18

Effect of investigations on clinical management

Ninety patients (90 per cent) underwent carotid endarterectomy. Reasons for conservative treatment in the other ten included angiographic evidence of less than 70 per cent stenosis plus no symptoms for over 6 months (four), occlusion (four), cerebral artery aneurysm (one) and diffuse disease unsuitable for endarterectomy (one). One patient died following angiography. A 79-year-old woman developed mesenteric ischaemia and subsequently died in the intensive care unit. There were no neurological complications. Findings on angiography could be considered to have revised decisions made after duplex findings alone in only four cases: the patient in whom an anterior communicating aneurysm was discovered, one in whom it was difficult to visualize the origin of the internal carotid and the two patients in whom less than 70 per cent stenosis was revealed. However, in the latter two patients, the fact that no symptoms had been experienced for over 6 months was more relevant than the differences in duplex and angiography.

Postoperative complications included stroke (one patient), transient ischaemic attack (two) and hypoglossal neuropraxia (one). The stroke and hypoglossal palsy had both resolved in 3 months' follow-up.

Discussion

The benefits of endarterectomy in symptomatic patients with high-grade carotid stenosis are clear. The North American trial[1] showed an absolute reduction of 17 per cent in the risk of ipsilateral stroke for symptomatic patients with 70–99 per cent stenosis. The European trial[2] showed a less substantial, but still significant, reduction in stroke risk for 70–99 per cent stenosis. The benefits for patients with less severe stenoses are unknown[3].

Both trials divided groups on the basis of angiographically defined degree of stenosis. The North American Symptomatic Carotid Trial (NASCET) compared the diameter of the stenotic lumen with that of the normal artery beyond the bulb whereas the European trial compared the diameter of the stenotic lumen with that of the presumed outline of the carotid bulb (*Fig. 1*). Both methods have been shown to underestimate the actual anatomical stenosis as measured by planimetric analysis of endarterectomy specimens[7]. Similarly, the European and North American methods and duplex all give significantly different results for identical stenoses[7].

Table 2 Patients considered for surgery where angiography and duplex findings were significantly different

Patient no.	Age	Sex	Indication	Duplex (% stenosis)	Angiogram (% stenosis)	Delay between scan and angiogram (weeks)
1	68	F	Amaurosis fugax	80	60	8
2	65	F	TIA	70	60	<1
3	54	M	Stroke	60	85	<1
4	61	M	Stroke	50	90	12
5	68	F	TIA	>90	Cerebral aneurysm	8
6	72	F	Stroke	Unclear	50	<1

TIA, transient ischaemic attack

Duplex provides the most accurate measurement compared with the excised specimen[7,8]. Other techniques such as magnetic resonance angiography (MRA) and spiral computed tomography (CT) are increasingly being employed[9].

In consideration of the best method of carotid assessment, important factors are accuracy of the investigation, morbidity of the technique, economic cost and effect on clinical management. In this study angiography has been used as the 'gold standard' since trials establishing the selection criteria for carotid endarterectomy have been based on angiographic measurements[1,2,10]. There was good agreement between angiography and duplex in defining degree of stenosis. Considering all 198 carotid arteries visualized (in 100 patients) by duplex the positive and negative predictive values were 96 and 98 per cent respectively for 70–99 per cent stenoses. There was no statistical difference between angiography and duplex in differentiating 70–99 per cent stenosis from less than 70 per cent stenosis or occlusion ($P = 0{\cdot}25$). Duplex and angiography placed 94 per cent of symptomatic stenoses in the same category. Given the delay in performing angiography, of up to 12 weeks, and improvements in imaging technology since 1992, a prospective study might now show these differences to be even smaller. Other studies have yielded similar results[11,12]. Mattos *et al.*[12] reported a sensitivity of 98 per cent and a specificity of 90 per cent for duplex imaging compared with angiography in defining a stenosis of greater than 50 per cent. While peak systolic velocity criteria have been employed in this study, some publications have proposed other methods. Moneta *et al.*[13] assessed a number of duplex methods of defining 70–99 per cent stenosis compared with the NASCET angiographic method and concluded that the internal carotid to common carotid peak systolic ratio gave the highest accuracy.

More important than comparison of measurements is the effect of these investigations on clinical management. While at present a 70 per cent stenosis in a symptomatic patient may be taken as a basis on which to offer carotid endarterectomy, this may change with further research. Of the ten patients not offered surgery relevant findings from angiography were a cerebral aneurysm, and a stenosis of less than 70 per cent in two patients. The importance of the cerebral aneurysm as a contraindication to carotid endarterectomy is arguable. Other studies support the finding that angiography rarely alters patient management; Matos *et al.*[12] found angiography affected clinical management in only 4 per cent of patients. Similarly, Dawson *et al.*[14], in assessing 94 carotid stenoses by angiography and duplex, found the latter to be diagnostic in 93 per cent of patients.

The risk of disabling stroke and death following arch angiography has been estimated as 1 and 0·06 per cent respectively[15]. The single death in this study emphasizes the significant risk of angiography, especially in light of the low overall complication rate following endarterectomy (1 per cent transient stroke in this study). While none of the patients undergoing angiography in this study suffered neurological complications, the recently published Asymptomatic Carotid Atherosclerosis Study[16] reported a stroke rate of 1·2 per cent following angiography. In comparison, duplex imaging is associated with no known morbidity, and is repeatable and cheap.

Factors other than the degree of internal carotid artery stenosis are important in determining the risk of stroke. Increasing evidence is now accumulating about the importance of plaque morphology, e.g. lipid content, continuity of fibrous cap and surface ulceration[17]. This information may affect the need for other methods of carotid assessment such as MRA. However, duplex appears to be well placed to provide accurate plaque imaging.

While duplex scanning has definite advantages over angiography with respect to associated morbidity and cost, there are instances when colour duplex assessment may be inadequate. A number of publications have reported difficulty in differentiating occlusion and tight stenosis[14]. Recent improvements in technology may have overcome this problem; Mattos *et al.*[18] reported 100 per cent accuracy of colour-coded duplex in defining carotid occlusion compared with angiography. The accuracy of duplex in defining occlusion may be improved by use of contrast enhancement[19]. Rarely, visualization of the carotid bifurcation can be hampered by a heavily calcified plaque[14], as in one patient in this study.

In most cases duplex imaging can now be used alone as an accurate, safe and cheap alternative to angiography. When duplex assessment is technically difficult arch angiography should be performed. In the future, spiral CT or MRA may be a safer alternative. Local audit of results is advised to confirm the applicability of these findings to other vascular laboratories.

Acknowledgements

The authors thank the Department of Neuroradiology, particularly Dr S. Halpin, for help with this study.

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British Journal of Surgery 1996, 83, 1238–1241

Homocysteine: an independent risk factor for the failure of vascular intervention

I. C. CURRIE, Y. G. WILSON, J. SCOTT*, A. DAY*, D. STANSBIE*, R. N. BAIRD,
P. M. LAMONT and W. G. TENNANT

*Departments of Vascular Surgery and *Chemical Pathology, Bristol Royal Infirmary, Bristol, UK*
Correspondence to: Mr I. C. Currie, Vascular Studies Unit, Level 7, Bristol Royal Infirmary, Bristol BS2 8HW, UK

Hyperhomocysteinaemia is an independent risk factor for the early development of arterial disease. Homocysteine and cardiovascular risk factors were assessed in 41 young and 25 older patients with vascular disease. As homocysteine may act by the generation of free radicals, total antioxidant capacity was measured. Hyperhomocysteinaemia was found in 29 per cent of patients but there was no difference between young and older patients. Homocysteine level was unrelated to other cardiovascular risk factors. Young age, diabetes and hyperhomocysteinaemia were independent risk factors for the failure of vascular procedures ($P = 0{\cdot}006$). Patients with hyperhomocysteinaemia had raised total antioxidant capacity. The potential of identifying and treating a subgroup of patients with a poor prognosis deserves further study.

Hyperhomocysteinaemia is a recently identified independent risk factor for the early development and progression of atherosclerotic lesions[1–3]. The congenital disorder homocysteinuria is associated with very high levels (greater than 100 μmol/l) of the thiol-containing amino acid homocysteine[4]. This condition is also associated with ocular and skeletal deformities, and death from severe atheromatous disease at an early age. Classically, homocysteinuria results from a homozygous enzyme deficiency of cystathionine β-synthase which irreversibly converts homocysteine to cystathionine[5]; patients heterozygous for this genetic disorder show moderately raised levels of plasma homocysteine. A number of congenital disorders of enzymes involved in homocysteine metabolism have also been identified as causing hyperhomocysteinaemia[5]. Vitamins B_6, B_{12} and folate are cofactors for homocysteine metabolism and acquired deficiencies may also result in mild hyperhomocysteinaemia[2,5–8]. A raised level of homocysteine has been proposed as a potentially treatable risk factor for the development of atherosclerotic disease at an early age[9,10].

The aims of this study were, first, to compare levels of serum homocysteine in a group of young patients undergoing vascular intervention for peripheral vascular disease with those of a group of older patients undergoing similar procedures and, second, to investigate the influence of homocysteine on the failure of peripheral vascular intervention. It is postulated that homocysteine may cause endothelial cell injury via a direct toxic effect and/or via generation of free radicals[11,12]. Free radicals are antagonized *in vivo* by antioxidants such as urate, α-tocopherol and glutathione. The association between homocysteine and serum total antioxidant capacity was, therefore, also investigated to look for evidence of depletion of antioxidants as a result of increased free radical generation.

Patients and methods

Using computerized databases, 55 patients were identified who had undergone either angioplasty or vascular surgery for lower-limb arterial disease at age 45 years or less at the time of attempted revascularization. Each patient was matched with an older control who had undergone a similar vascular intervention at approximately the same time. Of 83 surviving patients, 66 (three women) agreed to attend for outpatient review and are the subject of this study. The remaining 17 surviving patients were contacted but were either unwilling to attend or had moved out of the area.

Of the patients studied, 41 were young (median age 43 years) and 25 were older (median age 68 years) at the time of the original vascular intervention. Twenty-seven were current and 39 were ex-smokers. The procedures performed on the 66 patients are shown in *Table 1*; 11 were diabetic and 12 were hypertensive. Two patients had acute ischaemia, nine had critically ischaemic limbs and 55 were claudicants. All patients were thought to have atherosclerotic peripheral vascular disease on the basis of clinical findings and arteriography.

Case notes of all patients were reviewed. Failure of the initial revascularization procedure was diagnosed when preoperative symptoms returned with a fall in ankle:brachial pressure index to within 0·15 of the preoperative value. Requirement for a further revascularization procedure on the same limb or for amputation also indicated failure of the initial vascular procedure. All patients were followed up regularly in a vascular studies unit.

A clinical history was taken and ankle pressures determined. Carbon monoxide levels in expired air were measured using a Bedfont micro smokerlyzer (Bedfont Scientific, Upchurch, UK). Venous blood was taken from fasted patients, centrifuged, and a serum sample frozen at −70°C within 10 min. Full blood count, clotting screen, and measurements of plasma viscosity and serum fibrinogen level were carried out. Liver function tests were performed, serum levels of creatinine, urate, cholesterol and triglyceride were measured. Three patients were receiving warfarin therapy at the time of study, in one case for known

Table 1 Revascularization procedures in 66 patients

Procedure	*n*
Iliac angioplasty	27
Femoropopliteal angioplasty	13
Aortobifemoral bypass	8
Femorofemoral crossover bypass	8
CFA endarterectomy	1
Femoropopliteal/distal graft	7
Thrombectomy	2

CFA, common femoral artery

Paper accepted 11 December 1995

protein C deficiency. No patient was taking B_{12} or folic acid supplements.

Frozen serum samples were thawed to perform homocysteine and antioxidant assays. Homocysteine levels were measured by high-performance liquid chromatography (HPLC)[13,14]. Total serum concentrations were measured by first liberating homocysteine from protein and mixed disulphides. Liberated thiols were then derivatized with a fluorogenic reagent and 20 μl of the sample assayed by reverse-phase HPLC. Initial studies on 46 healthy laboratory staff (30 men, 16 women, age range 21–63 years) found a mean serum homocysteine concentration of 12·2 μmol/l for men and 10·4 μmol/l for women (95th centile values 18·0 μmol/l and 13·6 μmol/l respectively).

Total antioxidant capacity was determined using an enhanced chemiluminescent assay[15]. This involved a steady production of free radicals that react with luminol to cause light emission which was measured by a luminometer. Added antioxidants in serum cause a temporary quenching of free radical production, detectable as a reduction in light emission. High levels of antioxidants cause a more prolonged reduction in light emission. The method is calibrated using the synthetic tocopherol analogue Trolox (6-hydroxy-2,5,7,8-tetramethylchroma-2-carboxylic acid; Aldrich Chemical, Gillingham, UK).

Results

Patients aged 45 years or less represented 4·5 per cent of all those having lower-limb arteriography and 2·9 per cent of patients undergoing lower-limb revascularization operations. At the time of study, five young patients and 22 older controls had died, generally of cardiovascular disease. The duration of clinical and haemodynamic improvement following the initial revascularization procedure is shown in *Fig. 1* for the 66 patients studied. Four patients required amputation because of failure of vascular intervention; none of them had high levels of homocysteine. Of nine early failures within the first month, two were due to technical problems at angioplasty but in seven patients thrombosis of initially patent grafts or radiologically successful dilatations occurred. Four of these nine patients had hyperhomocysteinaemia. Nine patients had intermediate failure between 1 and 12 months after the procedure. In three of these, graft occlusion occurred because of intimal hyperplasia noted at revisional surgery. Five angioplasty sites restenosed and stenosis of the donor limb to a femorofemoral crossover graft occurred in one patient. Two of the nine patients with intermediate failure had hyperhomocysteinaemia. There were six late failures over a year after the original procedure. In two patients this resulted from disease progression and in three was due to disease recurrence at the site of a previous angioplasty. One patient had a late vein graft stenosis. Two patients with late failure had hyperhomocysteinaemia.

Homocysteine levels greater than the 95th centile for a normal healthy population were considered to be significantly raised. Levels in young and old patients are shown in *Fig. 2*. The incidence of hyperhomocysteinaemia was 29 per cent in all patients studied. There was no difference in homocysteine levels found in young and old patients ($P = 0{\cdot}46$, unpaired t test). Patients with hyperhomocysteinaemia had significantly higher creatinine and urate levels, and total antioxidant capacity than those with normal homocysteine levels. The prevalence of other cardiovascular risk factors was similar in patients with normal and raised levels of serum homocysteine (*Table 2*).

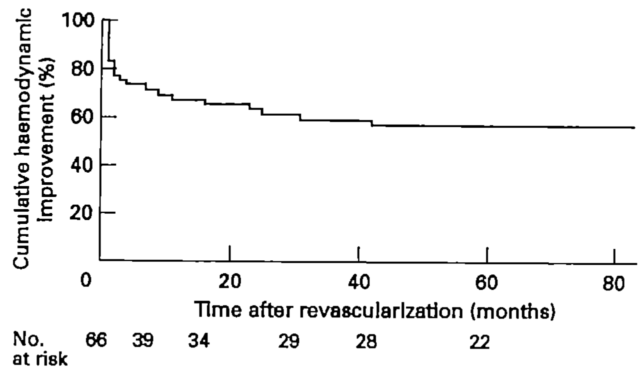

Fig. 1 Duration of haemodynamic improvement after revascularization

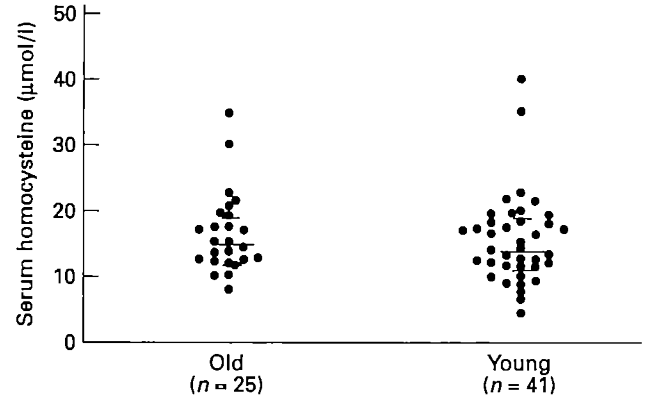

Fig. 2 Serum homocysteine level in young and old patients (bars represent median and interquartile range)

Table 2 Cardiovascular risk factors and related parameters in patients with normal and raised homocysteine levels

	Patients with normal homocysteine level	Patients with homocysteine level above above 95th centile	P*
No. of patients	47	19	
Serum cholesterol (mmol/l)	6·34	6·22	0·73
Serum triglycerides (mmol/l)	2·19	2·57	0·33
Serum fibrinogen (g/l)	4·21	4·34	0·71
Plasma viscosity (mPa/s)	1·72	1·74	0·44
Carboxyhaemoglobin (%)	1·72	1·93	0·72
White cell count ($\times 10^9$/l)	7·64	7·69	0·95
Serum urate (μmol/l)	357	456	0·001
Serum total antioxidant capacity (μmol/l)	475	566	0·007
Serum creatinine (μmol/l)	101	116	0·007

Values are mean. *Unpaired t test

Factors influencing the survival of the initial vascular procedure for all 66 patients undergoing blood tests were studied using multiple logistic regression. A Weibull survival model was assumed and the influence of age, diabetes, hypertension and biochemical variables on the survival of vascular procedures studied. Young age at intervention, diabetes and hyperhomocysteinaemia were significant, independent risk factors for the failure of vascular intervention ($P = 0{\cdot}006$, log rank test).

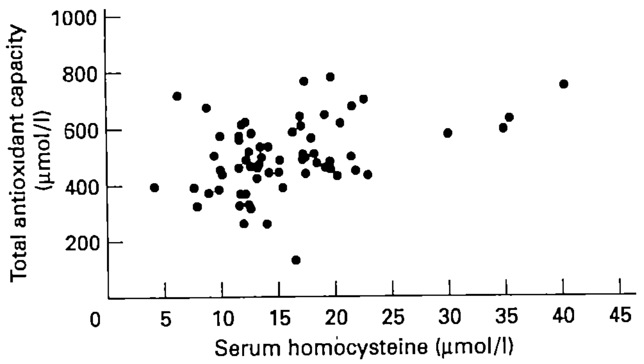

Fig. 3 Relationship between serum homocysteine and total antioxidant capacity ($r = 0{\cdot}37$, $P < 0{\cdot}01$)

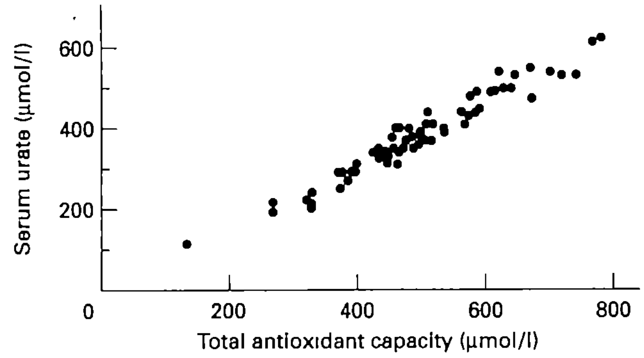

Fig. 4 Relationship between total antioxidant capacity and serum urate level ($r = 0{\cdot}97$)

The relationship between serum homocysteine level and total serum antioxidant capacity is shown in *Fig. 3*. Linear regression analysis shows a positive correlation between serum homocysteine and total antioxidant capacity ($r = 0{\cdot}37$, $P < 0{\cdot}01$).

The relationship between urate, a known antioxidant, and total antioxidant capacity, measured by the enhanced chemiluminescent assay, is shown in *Fig. 4*. Linear regression analysis shows that the correlation between urate and total antioxidant capacity is close ($r = 0{\cdot}97$). Urate levels may be raised by renal impairment and a positive association was found between serum urate and creatinine levels ($r = 0{\cdot}54$, $P < 0{\cdot}001$).

Discussion

The assay for direct measurement of total homocysteine proved to be robust, with good repeatability and accuracy[14]. Raised levels of homocysteine have been reported in patients developing premature arterial disease and screening for this abnormality has been advocated in young patients with vascular disease[10]. The upper 95th centile values established for healthy women and men were compatible with those of previous studies[1,2,7,14,16]. Boers *et al.*[17] found that 30 per cent of patients aged 50 or less with symptoms of cerebrovascular or peripheral arterial disease had raised peak levels of homocysteine after a methionine loading test. The reported incidence of hyperhomocysteinaemia ranges from 13 to 38 per cent[1–3,6,9,16,18]. The present finding of hyperhomocysteinaemia in 29 per cent of patients studied is thus consistent with previous reports. Taylor and colleagues[1] reported that raised levels of homocysteine, in a consecutive series of arteriopaths, were not related to age, supporting the findings in the present study[1]. However, Brattstrom *et al.*[8] and Molgaard and co-workers[2] reported that homocysteine levels tended to rise with increasing age.

Homocysteine has been shown previously to be associated with the development and progression of lower-limb arterial disease[1]. This study found that hyperhomocysteinaemia is an independent risk factor for the failure of vascular intervention. Furthermore, there was no significant difference in the levels of other known cardiovascular risk factors for patients with normal or raised levels of homocysteine, in agreement with previous findings[1,2,8,16]. Hyperhomocysteinaemia was found in patients with early failure due to thrombosis, in intermediate graft failure resulting from the development of vein graft stenoses, and in late failures due to progression of atheroslerotic disease.

Although the development of atherosclerotic lesions and the failure of peripheral revascularization procedures are pathologically different processes, there are similarities[19,20]. Endothelial cell injury may underlie both processes and may be caused by raised homocysteine levels. The pathogenesis associated with the adverse effects of homocysteine are unknown; indeed a direct causal relationship between hyperhomocysteinaemia and atherosclerosis has not been conclusively demonstrated *in vivo*. Patients with hyperhomocysteinaemia had higher creatinine levels than those with normal homocysteine levels. Brattstrom *et al.*[8] also found that serum homocysteine concentration correlated with creatinine level and postulated that impaired renal function may contribute to mild hyperhomocysteinaemia. However, only 13 of the patients undergoing blood tests had a serum creatinine level greater than 120 μmol/l.

It was surprising to find a weak positive correlation between serum total antioxidant capacity and homocysteine level in this study. If homocysteine exerts its pathological effects via the generation of free radicals, high homocysteine level might be expected to be associated with low total antioxidant capacity. However, both mild hyperhomocysteinaemia and raised serum urate (a known antioxidant) may result from renal impairment. Perhaps patients with advanced arterial lesions have a mild degree of renal impairment contributing to hyperhomocysteinaemia and raised urate, and thus antioxidant, levels. The total antioxidant capacity assay only measures aqueous antioxidants and may not relate to the antioxidant conditions operative *in vivo*. Lipid-soluble antioxidants such as α-tocopherol, present in cell membranes to prevent lipid peroxidation, may be important *in vivo* but are not measured by the technique.

Starkebaum and Harlan[21] reported that cultured endothelial cells were injured by hydrogen peroxide generated by copper-catalysed oxidation of homocysteine. Blom *et al.*[22] found that homocysteine levels were not related to malondialdehyde and concluded that lipid peroxidation was not significant in hyperhomocysteinaemia. Stamler and colleagues[23] postulated that homocysteine may react *in vivo* with nitric oxide to produce a compound with vasodilatory and antithrombotic properties. In summary, the pathogenesis of the apparently adverse effects of homocysteine on arterial disease remains unclear.

Acknowledgements

The authors thank Dr J. I. Gowers for statistical advice. Mr I. C. Currie was supported by grants from the Smith and Nephew Foundation and South Western Regional Health Authority

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British Journal of Surgery 1996, 83, 1242–1244

Operative results of House advancement anoplasty

S. M. SENTOVICH, P. M. FALK, M. A. CHRISTENSEN, A. G. THORSON,
G. J. BLATCHFORD and R. M. PITSCH

Department of Surgery, Section of Colon and Rectal Surgery, Creighton University School of Medicine, 601 North 30th Street, Omaha, Nebraska 68 131, USA
Correspondence to. Dr M. A. Christensen

A retrospective review of 29 patients who had an anoplasty using the sliding House advancement flap was carried out to evaluate the efficacy and safety of this new technique. Long-term symptom relief and late complications were determined by telephone interview. Indications for anoplasty were: stenosis (21 cases), ectropion (four), Bowen's disease (two), keyhole deformity (two) and perineal fistula (one). A single House flap was performed in most patients, but eight required multiple flaps. Lateral internal sphincterotomy was performed concomitantly in 16 of 21 patients with anal stenosis. Postoperative complications included donor-site separation (14), urinary retention (eight) and sepsis (four). At a median follow-up of 28 months, 26 of 29 patients had improved and 24 were completely satisfied. House flap anoplasty can be used to correct many anoderm deficiencies with a high rate of success and patient satisfaction.

Anal stenosis and ectropion are manifestations of a deficiency of anoderm. This usually follows a previous haemorrhoidectomy, ileal pouch–anal anastomosis, correction of an imperforate anus or excision of a premalignant or malignant perianal skin lesion. A deficiency of anoderm may be obvious immediately, for example, after excision of extensive Bowen's disease, or it may become apparent after many years, for example, when anal stenosis follows haemorrhoidectomy. Several flap procedures have been devised to correct anal stenosis, ectropion and other conditions associated with a deficiency of anoderm[1–16].

Simple random flaps receive their blood supply through a skin bridge to the dermal and subdermal vascular plexus in the flap. Examples of random advancement flaps include the Y–V[2,3] and mucosal advancement anoplasties[4]. More extensive random rotational flaps include the C anoplasty[5] for unilateral coverage and the S anoplasty[6] for complete lining of the anal canal.

Random full-thickness sliding advancement flaps lack a skin bridge and receive blood supply through unnamed vessels extending through a fatty pedicle from the underlying muscle. These include the V–Y anoplasty[7], the rectangular graft of Sarner[8], the U-shaped island flap[10] and the newly described 'House' advancement pedicle flap[11]. Recently, the authors have used the House advancement pedicle flap for all patients with anal stenosis, ectropion and other deficiencies of anoderm because its design and construction combine some of the best features of the other flap techniques. This study reviews the indications for, and operative results, postoperative complications and long-term function of, House flap anoplasty.

Patients and methods

The notes of 29 consecutive patients who underwent House flap anoplasty between December 1990 and April 1994 were reviewed Data collected included age, sex, indications for surgery and immediate postoperative complications. Long-term relief of symptoms, late complications and overall satisfaction were determined by note review and telephone interview with each patient in July 1994.

House flap anoplasty was performed as previously described[11]. Preoperative preparation consisted of a small enema but full mechanical bowel preparation was used when construction of multiple House flaps was anticipated. Perioperative antibiotics were not used. The patient was placed in the prone jack-knife position, a nasal speculum or small Ferguson retractor was placed in the anus and a longitudinal incision made in the right or left lateral position from the dentate line to the end of the stricture. Proximal and distal incisions were made perpendicular to the initial longitudinal incision (*Fig. 1*). Undermining the tissue edges of the longitudinal incision created a rectangular-shaped defect (*Fig 2*). A partial lateral internal sphincterotomy was performed if the internal sphincter muscle seemed to contribute to the stenosis. The 'walls' and 'roof' of the House flap were then incised, and the flap mobilized by dissection into the ischiorectal fat, avoiding undermining of the flap. When the flap could be easily advanced into the anal canal, it was sutured in place with 3/0 absorbable suture (*Fig. 3*). Patients with ectropion had it excised, and the resulting defect was filled with one or more House flaps. Stool softeners and sitz baths were prescribed after operation

Indications

House flap anoplasty was performed on 30 occasions in 29 patients over 3·5 years. Twenty women and nine men had the procedure, with a mean age of 60 (range 25–82) years. The indications for anoplasty are shown in *Table 1.* Stenosis most often occurred due to previous haemorrhoidectomy (16 cases) or ileal pouch–anal anastomosis (two). Ectropion occurred as a result of a haemorrhoidectomy, ileal pouch–anal anastomosis, vulvectomy with excision of the perianal skin, or correction of an imperforate anus.

The number of House flaps and concomitant use of a lateral internal sphincterotomy varied with the indications and findings at operation. Lateral internal sphincterotomy was added to 16 of 21 House flap procedures performed for anal stenosis. Ectropion and Bowen's disease usually required multiple House advancement flaps, and sphincterotomy was not performed. Multiple-quadrant flaps were placed diagonally to keep the incisions away from the midline.

Results

Median postoperative stay was 1 (range 1–11) days. The length of stay depended on the number of advancement

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Presented in part to the American Society of Colon and Rectal Surgeons in San Francisco, California, USA, June 1992
Paper accepted 16 October 1995

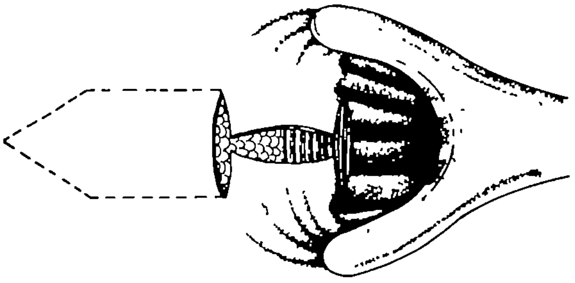

Fig. 1 Proximal and distal incisions made perpendicular to the initial longitudinal incision. (Reprinted with permission from *Dis Colon Rectum* 1992; 35: 201–3)

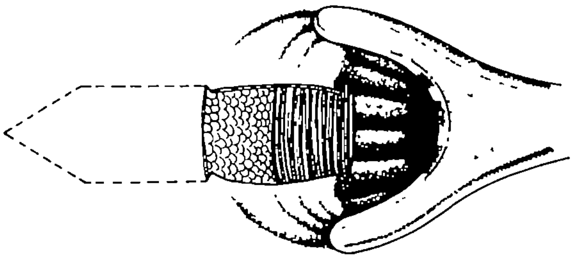

Fig. 2 The wound assumes a rectangular shape after undermining the edges. (Reprinted with permission from *Dis Colon Rectum* 1992; 35: 201–3)

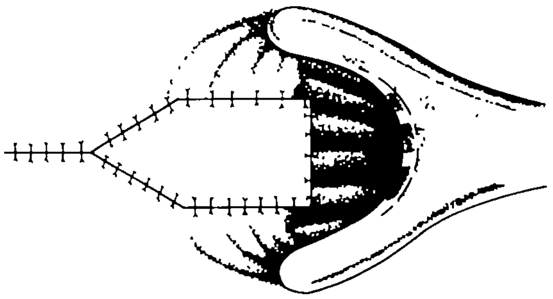

Fig. 3 Completed House flap advanced and sutured into place. (Reprinted with permission from *Dis Colon Rectum* 1992; 35: 201–3)

flaps performed. The two patients who underwent four-quadrant House flaps stayed in hospital for 7 and 11 days respectively.

Although there was no flap necrosis, recurrent stenosis, or recurrent ectropion, 20 patients had minor complications in the immediate postoperative period (*Table 2*). Donor-site wound separations were small and usually completely healed within 2 weeks. Postoperative septic complications included two urinary tract infections, one perianal streptococcal cellulitis, one perianal *Candida* infection and one *Clostridium difficile* colitis. One House flap retracted 5 days after operation, and required reoperation and replacement of the flap into the anal canal. Intermittent flatus and liquid incontinence developed in the two patients with Bowen's disease who required multiple House flaps. An unsuspected obstetric injury to both the internal and external anal sphincter was identified by postoperative transanal ultrasonography in one of these patients. Finally, House flap anoplasty failed to correct a perineal fistula in one patient.

Table 1 Indications for House flap anoplasty

Indication	No. of cases
Anal stenosis	21
Ectropion	4
Bowen's disease	2
Keyhole deformity	2
Perineal fistula	1

Table 2 Postoperative complications after House flap anoplasty

Complication	No. of cases
Donor site separation	14
Urinary retention	8
Septic complications	5
Incontinence (flatus and liquid)	2
Flap retraction	1

At a median follow-up of 28 (range 3–43) months, 26 of 29 patients had relief of preoperative symptoms and were able to discontinue stool softeners, laxatives and enemas after House flap advancement anoplasty. None of the patients with ectropion or keyhole deformity complained of further seepage or leakage after operation. Intermittent incontinence to both flatus and fluid persisted at 12 and 32 months after surgery in the two patients who underwent multiple House flaps for Bowen's disease.

Overall, 24 of 29 patients were satisfied with House flap anoplasty. Reasons for dissatisfaction in five patients included persistent pelvic pain not associated with the operation, occasional pain with defaecation despite relief of stenosis, stool urgency that did not occur after the operation, but after radiation therapy to the pelvis, severe pruritus in one of the scars after a four-quadrant House flap and recurrent perineal fistula after attempted House flap repair.

Discussion

The House advancement pedicle flap has been used for 29 consecutive patients with anal stenosis, ectropion and other deficiencies of anoderm. It combines the V–Y anoplasty[7] wound closure and Sarner's rectangular-sliding advancement flap[8]. It provides a long full-thickness section of anoderm based on vessels perforating from the underlying external anal sphincter. The rectangular base of the House flap is advanced proximally to provide coverage for the entire length of the anal canal. The outer triangular cut allows the donor site to be closed primarily in a V–Y fashion. Many high or long stenoses previously treated with multiple sphincterotomies, anal dilatation or extensive flap procedures may be more safely and simply treated by the House flap.

In this review, the House flap procedure successfully treated the primary problem in 26 of 29 patients. At a median follow-up of 28 months, 24 patients were completely satisfied. In patients with anal stenosis or ectropion treated with a diamond island flap, Pearl *et al.*[10] reported a good-to-excellent result in 92 per cent, and Pidala and colleagues[12] described an improvement rate of 91 per cent. Milsom and Mazier[13] noted good results in 90 per cent of patients undergoing a V–Y anoplasty or Y–V anoplasty for anal stenosis. In these three other studies, however, the type of flap varied depending on the particular diagnosis and circumstance. In the present series a similar success rate was achieved using only the House flap anoplasty for stenosis, ectropion and other conditions requiring new anoderm.

Few complications of the various anoplasty techniques have been reported. Khubchandani[14] reported a wound separation rate of 12 per cent after modified Martin anoplasty for stenosis in 41 patients, but did not describe any postoperative urinary tract problems. In other series, the perianal skin or donor-site wounds were left open, and consequently all patients required postoperative wound care. Both Pidala *et al.*[12] and Gingold and coworkers[2] closed the donor sites and noted wound separation rates of 18 and 36 per cent respectively. These series also reported urinary tract complications in 3–7 per cent of patients. On the basis of the published literature, the overall complication rate in the present series of 66 per cent, which included a wound separation rate of 47 per cent and a postoperative bladder catheterization rate of 27 per cent, seems to be high. These patients, however, differed from those in other studies in which a single flap for anal stenosis or ectropion was performed. In the series described here, five of 30 House flaps were done for indications other than stenosis or ectropion and eight were multiple. Multiple-quadrant House flaps were associated with a higher morbidity than a single flap. Other studies with limited follow-up reported no complications[3–5,7,9,13,15,16]. The present detailed study reporting complications in patients who were followed long term, emphasizes the need to inform patients before operation about potential wound, urinary tract and septic complications, especially when multiple flaps are anticipated. In addition, preoperative anorectal manometry and transanal ultrasonographic studies are now performed on women who may require multiple House flaps to detect occult sphincter injury.

House flap anoplasty is a simple, safe method to correct all types of anoderm deficiencies with a high rate of success and patient satisfaction. Its construction and design combine some of the best features of other flap repairs. It can be used in nearly any case in which there is a deficiency of anoderm.

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British Journal of Surgery 1996, 83, 1245–1246

Short note

p53 Mutations in primary colorectal adenocarcinomas and liver metastases

J. YAO, H.-S. GOH and D. R. SMITH

Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 169608
Correspondence to. Dr D. R. Smith

Point mutation of the p53 tumour suppressor gene is found in approximately 50 per cent of colorectal adenocarcinomas, with 98 per cent of point mutations falling within a 600-base-pair region of the messenger RNA, corresponding roughly to exons five to nine[1]. The majority of these point mutations consist of single base substitutions, leading to the incorporation of alternate amino acids in the p53 protein. Single base substitutions leading to non-sense or chain terminating codons are rare, although deletions or insertions leading to frame shift mutations are slightly more common[1]. Point mutation of the p53 tumour suppressor gene in colorectal adenocarcinomas has been shown to be associated with disease dissemination[2] and poor prognosis[3]. Metastatic disease is the primary cause of death in patients with colorectal cancer. The status of the p53 gene in metastatic liver deposits was therefore examined.

Materials and methods

Eight fresh liver secondary tumours were available for analysis. Each was histologically defined as a metastatic lesion from a primary colorectal adenocarcinoma. In six cases the primary tumour was also available for analysis. Point mutations of the p53 gene were detected initially by single stranded conformational polymorphisms, and mutations were then characterized by double stranded polymerase chain reaction cycle sequencing using a panel of primers as described elsewhere[4].

Results

Point mutations of the p53 gene were detected in seven of eight liver metastases tested. The remaining sample contained a deletion of one allele corresponding to codons 174–183 (*Table 1*). In the six cases in which the primary colorectal adenocarcinoma was also available for analysis, point mutations were detected in four samples. In each case where the primary adenocarcinoma contained a point mutation, the same point mutation was detected in the liver metastasis (*Table 1*).

Discussion

All metastatic liver deposits in this study evinced alterations of the p53 tumour suppressor gene. In seven cases point mutations were detected and in the eighth a deletion in one allele had occurred. These results are consistent with a recent report[5] also showing a high rate of p53 point mutation in hepatic metastases: a mutation rate of 77 per cent in metastases compared with 44 per cent in primary colonic adenocarcinomas. The presence of point mutations in the liver secondaries that were not found in the colorectal primary in both studies suggests that metastatic lesions can arise from subpopulations of cells that are not represented in the sample of the primary lesion. Furthermore, the high rate of mutation found in

Table 1 p53 Mutations in eight metastatic liver deposits and six corresponding primary colorectal adenocarcinomas

Sample	Organ	Mutation	Codon	Amino acid change
Patient 1				
Primary adenocarcinoma	Colon	TAC to TGC	163	Tyr to Cys
Secondary adenocarcinoma	Liver	TAC to TGC	163	Tyr to Cys
Patient 2				
Primary adenocarcinoma	Colon	ATC to AAC	254	Ile to Asn
Secondary adenocarcinoma	Liver	ATC to AAC	254	Ile to Asn
Patient 3				
Primary adenocarcinoma	Colon	TAT to TCT	205	Tyr to Ser
Secondary adenocarcinoma	Liver	TAT to TCT	205	Tyr to Ser
Patient 4				
Primary adenocarcinoma	Colon	—	—	—
Secondary adenocarcinoma	Liver	TAT to TCT	205	Tyr to Ser
Patient 5				
Primary adenocarcinoma	Colon	—	—	—
Secondary adenocarcinoma	Liver	TAT to TCT	205	Tyr to Ser
Patient 6				
Primary adenocarcinoma	Colon	CGC to CAC	158	Arg to His
Secondary adenocarcinoma	Liver	CGC to CAC	158	Arg to His
Patient 7				
Secondary adenocarcinoma	Liver	Deletion	174–183	—
Patient 8				
Secondary adenocarcinoma	Liver	CGG to TGG	248	Arg to Trp

Paper accepted 25 November 1995

the liver secondaries in both studies suggests that cells containing mutated p53 genes may demonstrate a selective advantage in establishing metastatic outgrowths. This report provides further evidence that mutation of the p53 tumour suppressor gene is one of the main factors determining behaviour of colorectal adenocarcinomas.

Acknowledgements

This work was supported by grants from The Lee Foundation, The Shaw Foundation and the Singapore Totalisator Board.

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British Journal of Surgery 1996, 83, 1247

Surgical workshop

Reduction of paraphimosis: a technique based on pathophysiology

V. RAVEENTHIRAN

Department of Surgery, Veer Surendra Sai Medical College, Burla, India

Correspondence to: Dr V Raveenthiran, 68 Seventh Street, Sayee Nagar, Madras 600 092, India

Paraphimosis is a painful condition that requires urgent surgical intervention. This paper describes a simple and effective technique of reduction based on the pathophysiology of the condition.

Surgical technique

Under penile block anaesthesia a tourniquet is applied to the shaft of the penis, proximal to the constricting ring of prepuce. With aseptic precautions a 20-g needle on a 10-ml syringe is thrust into the glans parallel to the urethra (*Fig. 1*). About 3–12 ml of blood is aspirated, depending on the size of the glans, until it collapses completely. The needle is withdrawn and firm squeezing pressure is applied to the glans using the pulp of the first three fingers. While maintaining the pressure, the tourniquet is released and the constricting ring of foreskin is gently reduced over the shrunken glans. Elective circumcision is subsequently performed.

Using this technique four patients with refractory paraphimosis were treated successfully without any complication. No tourniquet was used in the first case, and immediate refilling of the glans prevented effective aspiration. The technique was revised thereafter.

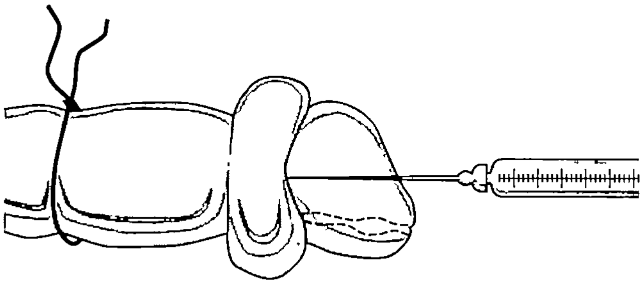

Fig. 1 Position of tourniquet and needle

Paper accepted 19 October 1995

Discussion

Emergency circumcision and dorsal slitting are the most reliable methods of relieving paraphimosis, but the prepuce is often oedematous, friable and infected so that it is technically difficult to achieve a good cosmetic result. Hence many surgeons prefer reduction of paraphimosis, reserving emergency operation for more difficult cases[1].

Whitaker's technique of elongation and squeezing the glans is considered the best method of reduction. Unfortunately this simple manoeuvre frequently fails as the constricting ring is often too tight to allow emptying of the glans. Many authors erroneously believe that the preputial oedema is the cause of irreducibility. Consequently several techniques for reducing the oedema have been proposed. These include puncturing the swollen foreskin[2], injection of hyaluronidase[3], application of hypertonic solutions[4] or ice packs[5], bandaging with a rubber strip, Southey tube drainage and manual massage[2]. It is to be remembered that the oedema is the result and not the cause of irreducibility. Hence attempts to dissipate the oedema are either useless or unnecessary.

In paraphimosis the constricting band of foreskin impedes venous return and causes glandular tumescence, which is the real hindrance for reduction[1]. It is always easier to aspirate blood than to squeeze it past a constricting ring. Aspiration of vascular spaces to produce detumescence is not new; it is an established method in the treatment of priapism[1]. This technique has also been successfully used to relieve strangulation of the penis by metal rings, which is identical to paraphimosis in its pathophysiology[6]. However the application of an aspiration technique in reducing paraphimosis has not been described in the literature. This technique is strongly recommended as a safe, simple and effective method of reducing paraphimosis.

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British Journal of Surgery 1996, 83, 1248–1251

Role of the general surgeon in a British trauma centre

I. M. BAIN, R. M. KIRBY, A. L. COOK*, P. A. OAKLEY† and J. TEMPLETON*

*Departments of Surgery, †Anaesthetics and *Orthopaedic Surgery, North Staffordshire Hospital and School of Postgraduate Medicine, University of Keele, Stoke-on-Trent, UK*

Correspondence to: Mr R. M. Kirby, Department of Surgery (M017), North Staffordshire Hospital, Stoke-on-Trent ST4 6QG, UK

A prospective audit of trauma patients seen or treated by the Department of General Surgery at the North Staffordshire Hospital Trauma Centre has been carried out, examining both the effect of a newly established trauma centre on overall workload and the outcome of patients admitted with severe injury. Trauma comprised approximately 2 per cent of the overall general surgical emergency workload. General surgeons were involved in the assessment of 25 per cent of severely injured patients but overall operated on fewer than 10 per cent of patients in this group. No patient died during the study period as a consequence of missed or inadequately treated intra-abdominal injury. These data suggest that there is insufficient work to justify specialist general surgical trauma surgeons in the UK. When general surgical intervention is required, however, it is usually vital and potentially life-saving.

A report[1] from the Royal College of Surgeons of England in 1988 recommended that certain patients with life-threatening injuries should have the opportunity of transfer to a specialized trauma centre. The report was based largely on the findings of a retrospective study of 1000 deaths from trauma[2] from 11 coroners' districts. This study revealed serious deficiencies in the management of seriously injured patients. Over 30 per cent of hospital deaths in severely injured patients were assessed as being potentially preventable; many non-neurological deaths occurred principally as a result of hypotension with delayed and/or inadequate surgical treatment. Two prospective studies[1,3] confirmed the finding of serious deficiencies in the management of severely injured patients and suggested that there could be survival benefits from sophisticated injury services. The College therefore proposed the instigation of trauma centres on a regional basis with all major surgical facilities on site, providing a 24-h service with surgical, anaesthetic and radiological staff of consultant level, together with their trainees. In July 1991 a pilot trauma centre was established at the North Staffordshire Hospital, Stoke-on-Trent, in a Department of Health study.

The North Staffordshire Hospital is a tertiary centre and is one of only seven hospitals in the UK with all surgical specialties including cardiothoracic surgery and neurosurgery on a single site. It serves a local population of 500 000. The trauma centre acts as a hub of the trauma system, serving a population of almost two million. Injured patients are either transported directly to the trauma centre by the ambulance services (land or air) or transferred from the five local district hospitals within the trauma system.

In North America, where trauma centres are established with improvements in patient management and survival[4,5], severely injured patients are usually admitted under the care of a trauma service, staffed by trauma surgeons, a subspecialty of general surgery. The pattern of trauma seen in most North American trauma centres is different from that in the UK, with a major proportion of admissions having penetrating injuries; for example, only 12 per cent of laparotomies performed at the Atlanta Trauma Center were for blunt trauma[6], compared with the UK where the majority of trauma is blunt. The results of a 1-year audit before the opening of the trauma centre at the North Staffordshire Hospital[7] showed that penetrating injury accounted for less than 5 per cent of all trauma (likewise only 8·9 per cent of patients admitted to the Royal London Hospital via helicopter had stab or gunshot wounds[8]). Although the Department of General Surgery was involved in the planning of the trauma centre, it was decided that there would be no attempt to assume the role of 'trauma surgeon'. Extra consultant posts were created in accident and emergency and anaesthetic departments, but the opening of the trauma centre coincided with changes in the on-call surgical rota involving reduction in the number of on-call junior staff.

The effect of the establishment of the trauma centre system on the work of the general surgeon has been examined both in terms of overall workload and, more specifically, with regard to assessment and operative intervention of severely injured patients. All patients received by the trauma team were studied to exclude those with missed or inappropriately managed abdominal injuries who might otherwise have been seen by a general surgical trauma surgeon.

Patients and methods

The general surgical trauma workload at the North Staffordshire Hospital was compared in the year before the establishment of the trauma centre (April 1989 to April 1990) and for 2 years (April 1992 to April 1994) afterwards.

Data were collected prospectively on every patient received following trauma Information was collected from trauma forms, patient's notes and medical staff. This included demographic data, details of all injuries, the patient's respiratory rate, systolic pressure and Glasgow Coma Scale on admission. The notes were checked for time of arrival at the centre, time of admission to operating theatre, operative details including grade of surgeon, involvement of different surgical teams and eventual outcome. Trauma death was defined as death occurring within 30 days of admission Post-mortem data were collected on all trauma deaths.

Severely injured patients were classified by the following criteria: Injury Severity Score (ISS) greater than 15 and/or a Revised Trauma Score (RTS) of less than 7·84. The ISS is based on the Abbreviated Injury Score devised by the Association for the Advancement of Automotive Medicine of the USA[9]. The

Paper accepted 14 December 1995

RTS was calculated using respiratory rate, systolic blood pressure and Glasgow Coma Scale recorded on arrival at the emergency department at the North Staffordshire Hospital or, in the case of transfers, at the emergency department of the referring hospital

All patients, both seriously and non-seriously injured, were initially assessed in the accident department by the trauma team. The trauma team was led by a resident consultant with a special interest in trauma management from the accident and emergency or anaesthetic departments; it included a registrar from the intensive care unit and a senior house officer or registrar from the accident and emergency department[10]. The senior registrar in general surgery was initially a member of the trauma team, but on review, his or her involvement was usually not necessary. Subsequently the general surgeon has been contacted, based on information relayed either by radio from the accident site itself or by the trauma team after identification or suspicion of injuries found in the primary and secondary surveys as in the Advanced Trauma Life Support (ATLS) protocol[11]. Protocols were established for investigation of the abdomen by diagnostic peritoneal lavage and abdominal ultrasonography. Peritoneal lavage was usually carried out by a general surgeon. Abdominal ultrasonography was performed by a radiologist at the request of either the trauma team leader or the general surgical team. The decision to operate was always made by the general surgeon There were four general surgical teams, each led by two consultants; five of the eight had ATLS training. Each team had one higher surgical trainee (registrar or senior registrar) and one basic surgical trainee.

Results

Overall admissions

The number of trauma admissions to the hospital in the years of the study has not changed significantly (*Table 1*). The number of severely injured patients (both ISS greater than 15 and RTS less than 7·84) increased by about 80 per cent since the introduction of the trauma centre, although the number of transfers from other hospitals did not change significantly. Blunt trauma was the mechanism of injury in over 95 per cent of patients with severe injury; over 50 per cent occurred as a consequence of road traffic accidents.

General surgical trauma admissions

The details of the general surgical overall emergency workload and the work related to trauma admissions are shown in *Fig. 1*. The work relating to severely injured patients is shown in *Fig. 2*. The emergency workload in general surgery remained busy but did not increase. Following establishment of the trauma centre the total number of trauma admissions increased by less than 50 per cent. Operations on all patients with trauma, both severely and non-severely injured, formed only a small proportion (approximately 2 per cent) of the overall emergency general surgical workload. Over 25 per cent of the severely injured were assessed by general surgeons compared with only 16 per cent before establishment of the trauma centre; most of those patients were seen during the initial resuscitation process in the accident and emergency department. In comparison, the majority of the severely injured were seen by the neurosurgical and orthopaedic teams; their involvement remained relatively unchanged. General surgeons were more often involved in the care of patients with penetrating injuries, the majority of which required operative intervention.

The type and number of general surgical operations performed on trauma admissions is shown in *Table 2*. Over 75 per cent of laparotomies on severely injured patients were performed within 4 h of admission (median 2·5 h (range from 10 min to 7 days)). Surgery was usually carried out for unexplained hypotension or suspected intra-abdominal injury detected by either abdominal ultrasonography or diagnostic peritoneal lavage. At most of the laparotomies significant intra-abdominal pathology was found warranting surgical intervention. Injuries found at laparotomy performed after 4 h included bowel injury,

Table 1 Overall trauma admissions (including skeletal and soft tissue)

	1989–1990	1992–1993	1993–1994
Total trauma admissions (severe and non-severe)	2506	2647	2769
Severely injured	138	251	227
ISS>15	114	170	184
RTS<7·84	24	81	43
Transfers	54	75	62

ISS, Injury Severity Score; RTS, Revised Trauma Score

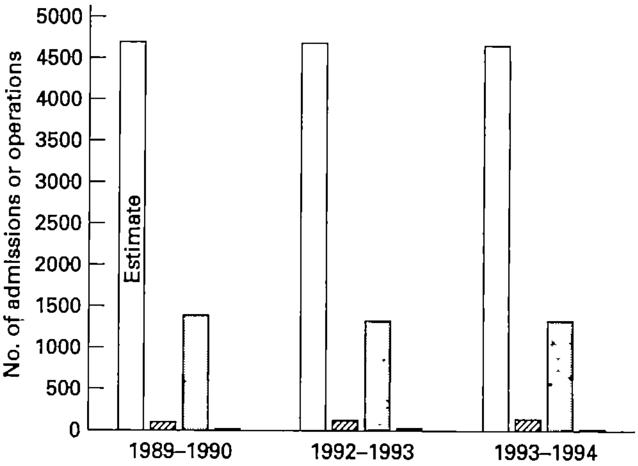

Fig. 1 General surgical emergency admissions and operations for the years of the study. □, Emergency admissions; ▨, trauma admissions; □, emergency operations; ■, trauma operations

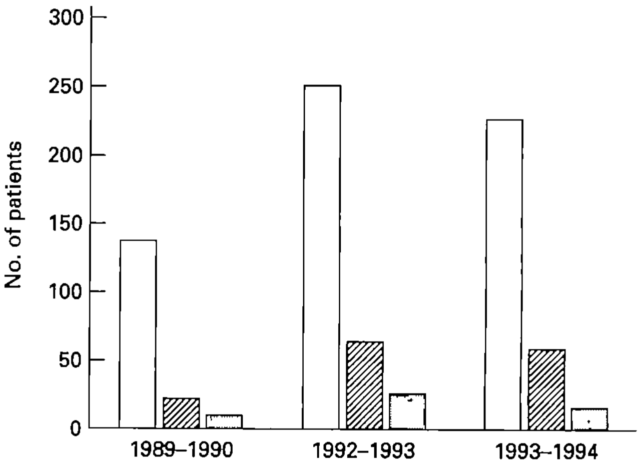

Fig. 2 General surgical intervention in severely injured patients. □, Total number of patients; ▨, assessed by general surgeon; □, general surgical operation

Table 2 Total number of laparotomies showing predominant injury at surgery and vascular procedures for the years of the study

	1989–1990	1992–1993	1993–1994
Severely injured			
Laparotomy (total)	10	24	13
No procedure	1	6	3
Splenectomy or repair	5	9	3
Liver repair	3	7	4
Retroperitoneal haematoma	1	2	2
Bladder injury	2	1	0
Bowel injury	0	3	1
Other	0	2	0
Vascular procedure	0	2	2
Non-severely injured			
Laparotomy (total)	10	6	6
Splenectomy	3	2	3
Liver repair	1	0	1
Bowel repair	2	0	0
Retroperitoneal haematoma	1	0	0
Stabbing	1	2	2
Negative laparotomy	2	2	0
Vascular procedure	2	0	3

Table 3 Deaths in 1992–1994

	n	Comment
Total no. of deaths	103	Includes two brainstem deaths with non-diagnosed intra-abdominal bleeding
Death during resuscitation	15	Includes one major intra-abdominal bleed and four less severe abdominal injuries
Death on table	2	Major hepatic trauma
Postoperative death	8	Four multisystem failures and four head injuries
Death after general surgical assessment (no general surgical operation)	16	No missed intra-abdominal trauma

delayed splenic rupture, suspected perforated bowel and iatrogenic splenic injury. Two patients had a laparotomy at another hospital before being transferred to the trauma centre for management of non-abdominal injuries.

Deaths

Between April 1992 and March 1994, 15 patients with multiple injuries (mean age 70 years) died during the initial resuscitation, before abdominal injury could be excluded (*Table 3*). Intra-abdominal injuries such as mesenteric tears were found at autopsy in four of these patients, but were not regarded as the primary cause of death. These patients had not been seen by the general surgical team. One patient died despite attempts at resuscitation following transfer from another hospital for neurosurgical assessment; the death was attributed to haemorrhage from splenic and renal injuries. Two patients admitted to the intensive care unit with severe head injuries were noted to have a probable abdominal injury but general surgical involvement was not requested because of brainstem death. In addition to the neurological injury in both patients, liver and splenic injuries and a renal haematoma with free blood were found at autopsy; these injuries were not thought to have contributed significantly to death by the forensic pathologist. Two young patients in extremis were transferred to theatre after initial thoracotomy in the accident and emergency department; both died from unsalvageable liver injuries.

Discussion

Since the establishment of the trauma centre there has not been a significant increase in the number of trauma patients seen in the emergency department, but the number of severely injured patients has increased by about 80 per cent. Although there were more transfers from other hospitals, most of the increase resulted from direct admissions. This reflects, in part, the changed protocols of the ambulance services.

The majority of the severely injured admissions had neurosurgical and/or orthopaedic injuries. General surgeons were involved in the assessment of over 25 per cent of these patients, being called immediately for penetrating injury or haemodynamically unstable patients. Abdominal ultrasonography may have been done before arrival of the general surgical team, but diagnostic peritoneal lavage was not performed before surgical review.

Even though the number of seriously injured patients assessed by general surgeons rose after the establishment of the trauma centre, the requirement for a general surgical opinion about possible abdominal injury and the need for surgery was not as high as expected. A combination of factors may be important: first, the increased experience of the admitting trauma team and, second, the increasing use of diagnostic abdominal ultrasonography in the accident and emergency department to exclude intra-abdominal injury. Experience of these diagnostic modalities for the detection and management of abdominal injuries is presently being evaluated[12].

When general surgical involvement is needed, it is usually because of intra-abdominal bleeding and is therefore required urgently. Fewer than 10 per cent of all the severely injured patients required general surgical operative intervention. Liver and splenic injuries were the commonest cause of intra-abdominal bleeding. A retrospective study of 1000 trauma deaths[2] showed that preventable deaths were due mainly to missed intra-abdominal bleeding rather than inadequate operative management. The decision whether to operate seems to be more important than the actual surgery itself. Negative laparotomies in patients undergoing other procedures concurrently are to be expected and should not be discouraged if significant intra-abdominal injuries are not to be missed. Despite the lack of a general surgeon in the initial trauma team, no patient died from an undiagnosed abdominal injury after admission to the trauma centre.

The low incidence of intra-abdominal and vascular injury reflects the pattern of trauma, which was blunt in over 95 per cent of cases. This was similar to the findings of the first report of the UK Major Trauma Outcome Study[13] and also mirrors the findings of a pre-hospital deaths study in North Staffordshire[14]. Road traffic accidents are the most common mechanism of injury. This differs from many centres in North America where penetrating injuries are common, forming up to 40 per cent of trauma admissions (F. Lewis, personal communication) and over 88 per cent of laparotomies[6]. The need for operative intervention by the trauma surgeon is also low (less than 20 per cent) after blunt trauma in North America. This is a reason given by surgical trainees in North America for the reduced interest in entering a career in trauma surgery[15,16].

The necessity for a trauma surgeon to see all patients with blunt trauma is being questioned in the USA. Recent studies[17–19] have shown that only a small minority of haemodynamically stable patients with blunt trauma require intervention by the trauma team. It was suggested that these patients should be assessed by the emergency room physicians with the trauma surgeon being called only when necessary. This is similar to the policy adopted at the North Staffordshire Trauma Centre.

The question has been posed whether the admitting trauma team should be led by a general surgeon, as initially suggested by the working part of the Royal College of Surgeons. The North Staffordshire model has demonstrated that this is not necessary, especially when general surgeons already have a busy workload. This need not be the only model: at the Royal London Hospital the driving force behind trauma care has been a general surgeon. The trauma team in London is led by a consultant or senior registrar in general surgery working on the principles of the advanced life support system; in the last 4-month interval 38 (58 per cent) of 66 patients admitted via helicopter had surgery[8]. Ten of these had general surgical procedures (details not given) compared with 22 orthopaedic and 15 neurosurgical operations. At the Toronto Trauma Centre[20], which sees a similar pattern of trauma to that in the UK, the team leaders are drawn from any specialty provided they have sufficient trauma training and experience. The team leader, as in North Staffordshire, refers patients to the appropriate specialty in theatre or on the admitting ward.

The lack of a single person in charge of the continued management of multiply injured trauma patients remains a matter of concern[21]. One advantage of trauma surgeons is that they can provide continued care of patients throughout their stay, including the intensive care unit. Residency programmes in trauma surgery therefore include specific intensive care training. In the UK few general surgeons have had specific training in intensive care management.

It may be argued that dealing with less than one severely injured patient requiring surgery per week does not result in the desired increase in operative experience in the management of patients with trauma. Despite the low numbers of patients needing general surgical assessment, working within a trauma system with a fixed resuscitation protocol has proved beneficial in providing surgical trainees with supervised experience of trauma management. To increase numbers further would require a significantly larger catchment area for the trauma centre. If this were to be adopted, a 24-h helicopter service with medical staff would be essential to prevent unacceptable transfer times. This would have considerable financial and staffing implications.

Because of the low overall number of trauma patients seen and the low incidence of general surgical operative intervention despite a two million catchment population, there is no pressing need for a subspecialty of trauma surgery within general surgery. General surgeons in the UK must maintain an active lead in improving trauma care and in carrying out further trauma research.

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British Journal of Surgery 1996, 83, 1252–1255

Randomized comparison of sitting and prone positions for stereotactic fine-needle aspiration breast biopsy

T. H. HELBICH, K. DANTENDORFER*, G. H. MOSTBECK, S. SCHICK,
P. WUNDERBALDINGER, M. AMERING*, R. ALEXANDROWICZ* and G. WOLF

*Departments of Radiology and *Psychiatry, University of Vienna, Waehringer-Guertel 18-20, A-1090 Vienna, Austria*
Correspondence to: Dr T. H. Helbich

In a prospective randomized study, 103 women had stereotactic biopsies performed either in the prone ($n = 51$) or sitting ($n = 52$) position. Questionnaires were administered before and after biopsy, to measure anxiety, pain and subjective experience in all patients. Vasovagal reactions were scored from 0 to 2 according to severity. There was no significant difference between biopsies performed in the sitting or the prone position with regard to overall tolerance. Significantly more patients biopsied in the prone position (15 of 51, 29 per cent) than in the sitting position (seven of 52, 13 per cent) would prefer premedication before a repeat biopsy ($P = 0{\cdot}04$). Of the total patient group, three women fainted, one in the prone position and two others in the sitting position. Breast biopsies performed in the prone or sitting position are equally well tolerated. Somatic reactions such as fainting are not a major problem during breast biopsy; however, attention should be focused on patient care, including information given before the procedure.

During the past decade, several studies have documented the effectiveness of screening mammography in the reduction of deaths from breast cancer[1–3]. The results of these studies have led to a substantial increase in the number of mammograms performed. In the USA, between 13 and 16 million mammographic examinations are performed annually[1,2]. Screening for breast cancer results in at least two benign excisional biopsies for every cancer detected[1,2,4]. The ratio of two benign to one malignant biopsies is the reverse of the current ratio in the UK[3]. The cost of surgical breast biopsy can exceed the cost of screening mammography[1,4,5]. Stereotactic biopsy guided by mammography or ultrasonography is now offered as an alternative diagnostic procedure[4–11]. The cost of stereotactic breast biopsy has been reported to be one-third to one-half that of excisional biopsy. Thus, the cost of breast cancer screening programmes could be reduced substantially[1,5–7].

Breast biopsy is considered safe and is normally well tolerated; however, there is some pain and anxiety associated with the procedure. Considering the high number of biopsies, studies of patient tolerance of the procedure are important. Stereotactic fine-needle aspiration biopsy (FNAB) can be performed with the patient in either the prone or the sitting position[5,8,9].

It is believed that biopsies performed on a seated patient are associated with a higher rate of adverse events, such as fainting, which lead to premature termination of the procedure. The purpose of this study was to compare the two different body positions for breast biopsy with regard to patient tolerance and rate of fainting.

Patients and methods

In this prospective study, 103 consecutive women (mean(s.d.) age 56(11·9) years) who were referred for cytological evaluation of suspicious lesions on mammography between January and September 1994 were assigned randomly to one of two different biopsy units. There were 52 women (mean(s.d.) age 56·6(11·1) years) investigated in the sitting position (Sterotix 2; GE Medical Systems, Milwaukee, Wisconsin, USA) and 51 women (mean(s.d.) age 56·4(12·1) years) assigned to the prone position (TRC-Mammotest, Täby, Sweden).

The details of stereotactic localization and FNAB have been described previously[7,10,11]. Briefly, each lesion was revisualized on the mammographic units. After verification of accurate needle placement, four aspirates were obtained in each case using a 20-G bevelled biopsy needle attached to a syringe. No local anaesthesia was required. All procedures were performed by a single radiologist (G.W.) with experience of more than 1000 FNAB procedures.

Patient questionnaires

Before and after biopsy, the patients were asked to complete the state–anxiety part of the Spielberger State–Trait–Anxiety inventory (range 20–80)[12]. The patients were also asked to complete questionnaires developed specially to assess their attitude toward the procedure before and after the examination (*Tables 1* and *2*). All patients received standard verbal information about the study and were informed that their answers to the questionnaires would not be made available to the clinical staff. In addition, the referring medical staff was not informed about the study to avoid additional information being given and to guarantee normal communication with the patients. Informed consent was obtained from all patients.

Vasovagal reactions

After the procedure all patients were asked if they had experienced a feeling of light-headedness or not. Light-headedness and fainting were scored by one radiologist (G.W.) as follows: 0, no reaction; 1, light-headedness; and 2, fainting causing termination of the procedure.

Statistical methods

Results were expressed as mean(s.d.). All statistical calculations were made using SAS (SAS Institute, Cary, North Carolina, USA)[13]. Group comparisons were done by means of Student's t test or the Mann–Whitney U test as appropriate. Frequency data were analysed with the χ^2 test or Fisher's exact test for small sample sizes. $P < 0{\cdot}05$ was considered significant. All P values were, where applicable, corrected for ties.

Paper accepted 30 November 1995

Table 1 Details and results of questionnaire completed before biopsy

	No. of patients	
	Sitting ($n = 52$)	Prone ($n = 51$)
The forthcoming examination makes me feel anxious		
Not at all	11 (21)	13 (25)
Somewhat	37 (71)	32 (63)
Very much	4 (8)	6 (12)
The forthcoming examination is important for my further medical treatment		
Not at all	2 (4)	1 (2)
Somewhat	12 (23)	11 (22)
Very much	38 (73)	39 (76)
I am worried about the outcome of the examination		
Not at all	4 (8)	5 (10)
Somewhat	28 (54)	22 (43)
Very much	20 (38)	24 (47)
The technical apparatus worries me		
Not at all	31 (60)	26 (51)
Somewhat	17 (33)	23 (45)
Very much	4 (8)	2 (4)
I have confidence in modern medicine		
Not at all	1 (2)	0 (0)
Somewhat	10 (19)	6 (12)
Very much	41 (79)	45 (88)
I am informed about the necessity of the examination		
Not at all	3 (6)	2 (4)
Somewhat	9 (17)	12 (24)
Very much	40 (77)	37 (73)
I am informed about the course of the examination		
Not at all	13 (25)	9 (18)
Somewhat	18 (35)	16 (31)
Very much	21 (40)	26 (51)

Values in parentheses are percentages. There was no significant difference in response between patient groups

Table 2 Details and results of questionnaire completed after biopsy

	No. of patients	
	Sitting ($n = 52$)	Prone ($n = 51$)
The examination was		
Easy to tolerate	39 (75)	41 (80)
Unpleasant	13 (25)	10 (20)
Hardly bearable	0 (0)	0 (0)
The duration of the examination was		
Easy to tolerate	43 (83)	36 (71)
Unpleasant	9 (17)	15 (29)
Hardly bearable	0 (0)	0 (0)
The body position during the examination was		
Easy to tolerate	37 (71)	32 (63)
Unpleasant	15 (29)	17 (33)
Hardly bearable	0 (0)	2 (4)
The pain sensation during the examination was		
Easy to tolerate	44 (85)	38 (75)
Unpleasant	8 (15)	12 (24)
Hardly bearable	0 (0)	1 (2)
The inability to move was		
Easy to tolerate	38 (73)	32 (63)
Unpleasant	14 (27)	18 (35)
Hardly bearable	0 (0)	1 (2)
The radiographer's care was		
Friendly	51 (98)	50 (98)
Correct	1 (2)	1 (2)
Unfriendly	0 (0)	0 (0)
The doctor's care was		
Friendly	48 (92)	45 (88)
Correct	4 (8)	5 (10)
Unfriendly	0 (0)	1 (2)
In comparison to my expectation the examination was		
More comfortable than expected	40 (77)	34 (67)
As expected	11 (21)	15 (29)
Less comfortable than expected	1 (2)	2 (4)
If necessary I would undergo such an examination once more		
Yes	50 (96)	47 (92)
No	2 (4)	4 (8)
If I had to undergo such an examination once more I would take an anxiolytic		
Yes	7 (13)	15 (29)
No	45 (86)	36 (71)*

Values in parentheses are percentages. *$P = 0{\cdot}04$ *versus* sitting position. There were no other significant differences between patient groups

Results

Before the procedure

Answers to the questionnaire completed before biopsy were not significantly different between the two groups, indicating that they were not biased by the selection method (*Table 2*).

Anxiety ratings

Anxiety ratings before the procedure were not significantly different between the two groups (mean(s.d.) 50·6(10·8) *versus* 51·2(10·3) for prone *versus* sitting position). After FNAB the anxiety levels significantly decreased in all patients ($P = 0{\cdot}0001$); there was no significant difference between the groups (mean(s.d.) 43·5(8·8) *versus* 44·4(8·5) for prone *versus* sitting).

Tolerance of the procedure

Responses to the questionnaire given after the biopsy are shown in *Table 2*. The questionnaires revealed that 39 of 52 patients biopsied in the sitting position and 41 of 51 examined in the prone position rated the examination easy to tolerate, 92 and 96 per cent respectively said they would undergo this examination again, if necessary. Significantly more patients biopsied in the prone position (15 of 51, 29 per cent) than in the sitting position (seven of 52, 13 per cent) stated that they would like to take an anxiolytic before a repeat biopsy procedure ($P = 0{\cdot}04$). The anxiety level, pain rating and motor unrest of patients wishing premedication for a repeat examination were not significantly different from those in patients who did not want premedication for a subsequent biopsy.

Vasovagal reactions

Two patients in the sitting position and one in the prone position fainted, which led to premature termination of the procedure ($\chi^2 = 3{\cdot}42$, 2 d.f., $P = 0{\cdot}18$). Three women had light-headedness in the sitting position. The incidence of adverse events was not significantly different between the two positions with respect to light-headedness and fainting, and for the two reactions combined ($P = 0{\cdot}11$, Fisher's exact test). Comparing the six women with scores of 1 and 2 with those with scores of 0, there was no significant difference in anxiety level, pain rating or response to the questionnaires. Fainting reactions were treated by placing the patient in the supine position and elevating the legs. Three patients with light-headedness needed no more than relaxation in a chair after the procedure. All vasovagal episodes were recognized by the staff and no patient was injured by falling.

Discussion

The results of this study suggest that breast biopsies performed either in the sitting or prone position are equally well tolerated. There were no significant differences between patient groups regarding anxiety, overall tolerance of the procedure and occurrence of vasovagal reactions.

Although breast biopsy is common, little is known about patient attitude toward this procedure performed either in the prone or sitting position[5,8,9]. The success of this invasive procedure is linked closely to the patient's attitude during the investigation. There are a number of factors that influence patient attitude toward a breast biopsy, including anxiety, pain and tolerance.

Various studies describe increased anxiety levels in anticipation of unpleasant situations in connection with medical investigations[14,15]. In this study, a high level of anxiety before the procedure did not influence the frequency of motor unrest, level of pain or rate of fainting, independent of patient position. This finding is supported by others who report that prescan anxiety level does not correlate with prematurely terminated magnetic resonance imaging (MRI) scans[15] and does not lead to an increase in motion artefacts on MRI scans[14]. Thus, a high anxiety level before the investigation does not have a negative influence on patient tolerance of the procedure. Not surprisingly, after the biopsy the anxiety level decreased significantly in both groups.

Pain has an important role in patient attitude during a medical procedure[16–18]. However, pain is not only influenced by the personality and constitution of the patient but also by previous experiences, anxiety, motivation, information, and care and personal interaction between the patient and medical staff[16–20]. In this patient population, 85 per cent of patients in the sitting position and 75 per cent of those in the prone position scored pain as easy to bear during the breast biopsy. Local anaesthesia does not improve patient tolerance in needle localization of the breast[21], although these results are disputed[22]. In addition, it has been shown that complications such as fainting occur independently of the type of interventional procedure performed in the breast either with, or without, use of local anaesthesia[5,8,9–11,21,23]. The finding that pain is not a factor influencing patient tolerance compares favourably with the results of Reynolds *et al.*[21].

It has been argued that biopsy performed in the sitting position increases the number of vasovagal reactions and premature terminations of the procedure. This study identified no significant difference in the occurrence of vasovagal reactions between groups. The six patients with light-headedness and fainting did not differ significantly from the rest of the patient population with regard to their anxiety and pain level as reported in the questionnaires. These results are similar to those reported in the literature for different breast biopsy and interventional techniques (*Table 3*)[5,8,9,21,23]. Even if, with a larger patient population, there should be a difference between the groups, the number of patients who develop problems is so low that as far as clinical management is concerned it is not of great significance.

In this study, breast biopsies performed either in the sitting or prone position were equally well tolerated. Of these patients, 92–96 per cent would undergo such an examination again; this is comparable to the reported 3 per cent of patients who think that diagnostic mammography is an intolerable procedure[18]. However, 22 patients stated they would want anxiolytic premedication if they had to undergo a repeat biopsy. This subgroup of patients did not differ significantly in level of anxiety, pain and motor unrest compared with the rest of the study population. Significantly more patients biopsied in the prone position stated that they would like to be premedicated before a repeat examination. Although the reason for this difference in patient tolerance is speculative, it might be explained by the body position. The fact that patients biopsied in the prone position cannot see what is going on might lead to a feeling of helplessness during the procedure. Fear of losing control during a medical examination is well known[24,25]. Anxiolytic premedication increases tolerance and improves results of MRI[26]. In addition to anxiolytic premedication, alternative interventions should be considered to improve patient tolerance to breast biopsy such as providing improved information about the procedure, and using breathing

Table 3 Vasovagal reactions reported in different interventional breast biopsy procedures

Reference	Year	No. of patients	Vasovagal reactions	Body position	Technique
Goldberg *et al.*[23]	1983	47	1 (2)	Sitting	Wire localization
Parker *et al.*[5]	1990	30	2 (7)	Sitting	Core biopsy (14 G)
		73	0 (0)	Prone	Core biopsy (14 G)
Helvie *et al.*[9]	1991	370	27 (7)	Sitting, prone	Wire localization ($n = 203$), FNAB ($n = 167$)
Reynolds *et al.*[21]	1993	89	1 (1)	Sitting	Wire localization
Caines *et al*[8]	1994	254	4 (2)	Sitting	Core biopsy (16 G, 18 G)
Present results	1996	52	2 (4)	Sitting	FNAB
		51	1 (2)	Prone	FNAB

Values in parentheses are percentages. FNAB, fine-needle aspiration biopsy relaxation techniques before the examination or playing music during the investigation[19,27–30].

Patient tolerance in breast biopsy procedures with regard to anxiety before and after the investigation, pain and motor unrest is high. The present results suggest that breast biopsy is equally well tolerated in the prone and sitting position. However, patient care with regard to information given before the procedure and control of anxiety is important.

Acknowledgements

This study was supported in part by the Ludwig-Boltzmann Institute for Radiologic Tumour Research.

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British Journal of Surgery 1996, **83**, 1256–1257

Short note

Management of premenopausal women with primary breast cancer

C. B. J. WOODMAN, J. SINGLETON,
J. COYNE* and A. BAILDAM†
*Centre for Cancer Epidemiology, Christie Hospital National Health Service Trust, Withington, Manchester, Departments of *Pathology and †Surgery, Withington Hospital, Manchester, UK*
Correspondence to: Professor C. B. J. Woodman, Centre for Cancer Epidemiology, Christie Hospital National Health Service Trust, Kinnaird Road, Manchester M20 9QL, UK

In 1992, the report by the Early Breast Cancer Trialists' Collaborative Group on the systemic treatment of early breast cancer by hormonal, cytotoxic and immune therapy suggested that the use of chemoendocrine adjuvant therapy could result in a 30–40 per cent proportional reduction in mortality rate for middle-aged women with primary operable breast cancer[1]. The present paper is the first population-based survey of the management of breast cancer in premenopausal women since the 1992 publication.

Patients and methods

All women aged 50 years or less with primary breast cancer diagnosed between 1 January 1993 and 31 June 1993 were identified from records held by the North Western Regional Cancer Registry. Clinicopathological and therapeutic details were obtained from casenote review. Women were considered to have had adjuvant chemoendocrine therapy if treated with tamoxifen, polychemotherapy (cyclophosphamide/methotrexate and 5-fluorouracil or adriamycin) or had an induced menopause within 3 months of the primary surgical procedure. Axillary sampling was considered inadequate when histological examination of axillary tissue revealed either the presence of axillary fat alone or fewer than four benign axillary lymph nodes. Any positive lymph node was regarded as adequate staging, but at least four negative nodes were required for the patient to be considered node-negative[2]. During the study, hospitals that treated fewer than ten women with invasive cancer in this age group were arbitrarily considered as low-throughput units and those treating ten or more as high-throughput units.

Results

Some 257 women aged 50 years or less with a primary diagnosis of breast cancer were identified. Patients excluded from subsequent analyses included 33 who were peri- or postmenopausal, four with inoperable, locally advanced disease, four with distant metastases and 15 with *in situ* disease alone. Casenotes of four patients were untraceable. Mean age of the remaining 197 patients was 41 (range 24–49) years. Details of primary surgery, tumour histology, axillary node status and use of chemoendocrine therapy are shown in *Table 1*. Primary surgery was undertaken in 26 hospitals. The median number of patients treated in each unit was 12 (range 1–22); 66 women (33·5 per cent) with invasive disease were treated in low-throughput units and 131 (66·5 per cent) in high-throughput units.

Table 1 Primary surgery, tumour histology, axillary lymph node status and use of chemoendocrine therapy

	No.
Primary surgery ($n = 212$)	
Mastectomy	115 (54·2)
Wide local excision and radiotherapy	83 (39·2)
Wide local excision alone	14 (6·6)
Histological type ($n = 212$)	
Infiltrating ductal carcinoma	162 (76·4)
Ductal carcinoma *in situ*	13 (6·1)
Invasive lobular carcinoma	16 (7·5)
Tubular carcinoma	9 (4·2)
Medullary carcinoma	4 (1·9)
Mucoid carcinoma	2 (0·9)
Invasive cribriform carcinoma	2 (0·9)
Lobular carcinoma *in situ*	2 (0·9)
Phyllodes	1 (0·5)
Invasive spindle cell	1 (0·5)
Tumour size (cm) ($n = 197$)*	
<1	22 (11·1)
$1–\leq 3$	127 (64·5)
>3	22 (11·1)
Not recorded	20 (10·2)
Not evaluable†	6 (3·0)
Grade ($n = 162$)‡	
I	16 (9·9)
II	57 (35·2)
III	81 (50·0)
Not recorded	8 (4·9)
Axillary lymph node status ($n = 197$)	
Node-positive	74 (37·6)
Mean (range) no. of nodes sampled	4 (1–25)
Nodes-negative	88 (44·7)
Mean (range) no. of nodes sampled	8 (4–22)
Inadequate sampling	12 (6·1)
Sampling not attempted	23 (11·7)
Use of adjuvant chemoendocrine therapy ($n = 192$)§	
No adjuvant therapy	46 (23·9)
Tamoxifen alone	64 (33·3)
Chemotherapy and/or tamoxifen	72 (37·6)
Ovarian suppression and/or tamoxifen and/or chemotherapy	10 (5·2)

Values in parentheses are percentages unless otherwise stated. *Women with invasive disease; †those with multifocal disease (two), indiscrete lesion (two) and fragmented specimen (two); ‡those with only infiltrating ductal carcinoma; §exclusions (three refused chemotherapy and two received neoadjuvant therapy)

Fifty-one (77 per cent) and 111 (84·7 per cent) women with invasive disease managed in low- and high-throughput units respectively, had adequate axillary sampling; this difference was not significant ($\chi^2 = 1{\cdot}67$; 1 d.f., $P > 0{\cdot}05$). However, only nine women with positive axillary nodes managed in a low-throughput unit received adjuvant chemotherapy, compared with 53 with positive axillary nodes managed in high-throughput units ($\chi^2 = 11{\cdot}4$; 1 d.f., $P < 0{\cdot}001$). Tumour grade and size were recorded in 42 (81 per cent) and 99 (93 per cent) women with evaluable infiltrating ductal carcinoma (IDC) managed in low- and high-throughput units respectively ($\chi^2 = 5{\cdot}8$; 1 d.f., $P < 0{\cdot}05$). Only nine women who were

Paper accepted 26 December 1995

node-negative with a grade III IDC lesion and none with a tumour more than 3 cm in size received adjuvant therapy. Node-negative women who received chemotherapy were younger (median age 35 years) than those who did not (median age 45 years).

Discussion

The appropriate treatment of primary breast cancer requires identification of women at high risk of metastatic disease[3,4]. Some 82·2 per cent of women in this series had adequate axillary node sampling but the risk status of 17·8 per cent could not be defined because of failure to sample axillary lymph nodes or to describe the size and grade of the primary tumour. It is impossible to opine on the subsequent treatment of these women.

A casenote review cannot always determine when comorbidity or patient preference has caused a deviation from best practice guidelines, but it is disturbing that 12 (16 per cent) women with positive axillary lymph nodes did not receive adjuvant chemotherapy. The optimal management of node-negative disease is less certain, but recent recommendations suggest that some patients with grade III disease or tumours more than 3 cm in size might benefit from adjuvant therapy[5].

The differences between low- and high-throughput units were related not to the willingness of surgeons to sample the axilla, but to the adequacy of pathological reporting and the delivery of adjuvant chemotherapy to high-risk women. Resetting the arbitrary throughput cut-off at a higher level accentuated differences between low- and high-throughput units.

The adoption of good practice guidelines offers the best prospect for improving survival from breast cancer. Progress towards this objective can be measured only by population-based surveys that reflect the totality of clinical management in a defined population.

The findings of this survey suggest that the recommendations of the Early Breast Cancer Trialists' Collaborative Group have not yet been uniformly adopted.

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Short note

Altered lymphatic drainage after lymphadenectomy or radiotherapy of the axilla in patients with breast cancer

C. I. PERRE, C. A. HOEFNAGEL*,
B. B. R. KROON, F. A. N. ZOETMULDER
and E. J. T. RUTGERS

*Divisions of Surgical Oncology and *Nuclear Medicine, The Netherlands Cancer Institute (Antoni van Leeuwenhoek Huis), Amsterdam, The Netherlands*

Correspondence to: Dr C. I. Perre, Department of Surgery, Diakonessenhuis, Bosboomstraat 1, 3482 KE Utrecht, The Netherlands

The incidental occurrence of lymph node metastasis in the contralateral axilla after previous treatment of breast cancer raises the question of whether these metastases derive from the original ipsilateral cancer or from a clinically occult contralateral cancer.

A lymphoscintigraphic study was performed to investigate regional lymphatic drainage patterns of the breast and chest wall before and after axillary dissection or radiotherapy.

Patients and methods

Twenty-three patients with operable breast cancer underwent regional lymphoscintigraphy before treatment. Two patients had clinically suspected ipsilateral involved lymph nodes; none had suspected contralateral nodes. Scintigrams of the chest and axillary regions were obtained 1 and 4 h after subcutaneous administration of 37 MBq (1 mCi) ^{99m}Tc-microcolloid in the medial part of the affected breast, using a large field of view γ camera with a low-energy high-resolution collimator, acquiring counts over 5 min.

The locoregional treatment of the 23 patients consisted of a modified radical mastectomy including axillary dissection (13 patients), breast-conserving treatment including an axillary dissection (eight), wide excision and irradiation of the axilla (one) and irradiation of the breast and axilla (one).

About 6 months after initial treatment, lymphoscintigraphy was repeated in all patients. The radionuclide was again injected in the medial part of the breast or, after mastectomy, cranial to the scar in the mid-clavicular line. Patients were entered in this study only if no clinical signs of recurrence were present at the time of the second scintigram.

Results

Lymphoscintigraphy before treatment

In three of the 23 patients no uptake of radioactivity was seen. In the remaining 20 patients uptake was observed in the ipsilateral nodes (axilla, 19; internal mammary chain, six). Only one patient revealed drainage to the contralateral axilla (*Table 1*).

Lymphoscintigraphy after treatment

In 12 patients no lymph node uptake was seen. In the remaining 11 patients activity was detected in the ipsilateral nodes, in the axilla in two and internal mammary chain in eight. Crossing over to the contralateral nodes was observed seven times in six patients (axilla, six; internal mammary chain, one) (*Table 1*), including the patient who showed contralateral drainage before surgery. Crossing over to the contralateral axilla developed after axillary dissection (four patients) or irradiation of the axilla (one).

Table 1 Regional lymphoscintigraphy before and after treatment in 23 patients with primary breast cancer

	Ipsilateral		Contralateral	
	Axilla	Internal mammary chain	Internal mammary chain	Axilla
Before treatment	19	6	0	1
After treatment	2	8	1	6

In some patients the scintigram showed uptake at more than one station

Discussion

Contralateral lymphatic drainage from the breast occurs occasionally[1,2]. If the normal routes of drainage are blocked by metastases retrograde lymphatic spread to the opposite axilla may occur[3]. However, the one patient in the present study with preoperative contralateral drainage had no axillary lymph node metastases.

The phenomenon of altered lymphatic drainage and crossing over following lymphadenectomy has been reported in melanoma of the lower limb[4]. Lymphatic drainage to the opposite axilla in patients after mastectomy has been shown before, but this was a selected group of patients with lymphoedema of the arm[5]. The present study confirms this observation, although none of the patients had oedema at the time of scanning.

The present observation of altered lymph flow and crossing over offers an explanation of why contralateral axillary metastasis may occur. Because of the altered lymphatic pathways, these nodes should be regarded as having become part of the regional nodes. Particularly in patients with local recurrence of breast cancer, treatment of the contralateral axillary metastasis together with the local recurrence should be considered.

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Paper accepted 10 December 1995

British Journal of Surgery 1996, 83, 1259

Case report

Duplicated vermiform appendix

K. T. KJOSSEV and J. E. LOSANOFF

Department of Emergency Surgery, Military Medical Academy, Sofia, Bulgaria

Correspondence to. Mr J E. Losanoff, PO Box 159, 1606 Sofia, Bulgaria

Duplicated vermiform appendix is rare: only about 60 cases have been described in the literature[1]. A unique case with atypical localization of the second appendix at the splenic flexure is reported.

Case report

A 32-year-old man presented with continuous left upper abdominal pain of 11-h duration. He was nauseated but had not vomited and had had a normal bowel movement the night before admission. Body temperature was 37·9°C, pulse 96 beats per min, respiratory rate 28 per min and blood pressure 150/90 mmHg. Examination was unremarkable except for tenderness in the left upper abdominal quadrant. Laboratory values were all within normal limits except for a leucocytosis of $14 \cdot 6 \times 10^9$ cells/l. Chest and abdominal plain films and abdominal ultrasonography were normal.

Following admission the patient remained stable but febrile. The pain increased, the abdomen became more tender and the white blood cell count increased to $18 \cdot 1 \times 10^9$/l. Midline laparotomy was performed, and a gangrenous vermiform appendix was found arising from the antimesenteric aspect of the left colic (splenic) flexure; it was approximately 8 cm long. The mesoappendix arose from the mesocolon inferiorly. Appendicectomy was performed in the usual manner. No other intra-abdominal pathology was observed, but a normal vermiform appendix was found in a typical anatomical position and a second appendicectomy was performed. The abdomen was drained. After an uneventful recovery the patient was discharged 7 days later.

Discussion

Duplication of the vermiform appendix is extremely rare; it is found in only 0·004 per cent of patients operated on for acute appendicitis[2]. In the authors' department this has been the only case of vermiform appendix duplication among 10 956 appendicectomies performed between 1965 and 1995, representing 0·009 per cent of all appendicectomies.

According to the classification of Cave[3], modified by Wallbridge[4], there are three main types of duplication: A, B (subdivided into B1 and B2) and C; in 1993 Biermann *et al.*[2] proposed an additional subtype, B3 (*Fig. 1*). To the best of the authors' knowledge, a second vermiform appendix arising from the splenic flexure has not been described previously. This localization may be classified as a B4 subtype.

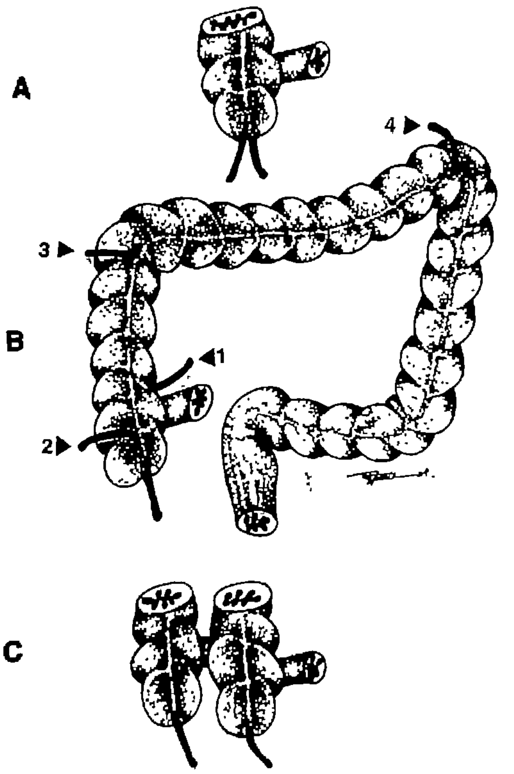

Fig. 1 Schematic drawing illustrating the classification of all known types of vermiform appendix duplication according to Cave[3], Wallbridge[4], Biermann *et al.*[2] and the authors' own observation. Type A, incomplete duplication with both appendices having a common base; type B, complete duplication with the first appendix arising from the caecum where all three taeniae join and the second appendix arising as follows: contralaterally from the caecum (B1), more distally from the ascending colon (B2), from the hepatic flexure (B3) and from the splenic flexure (B4); type C, complete duplication of the caecum, each caecum having its own appendix

Paper accepted 14 December 1995

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British Journal of Surgery 1996, 83, 1260–1262

Prospective comparison of laparoscopy, ultrasonography and computed tomography in the staging of gastric cancer

D. A. STELL, C. R. CARTER, I. STEWART* and J. R. ANDERSON

*University Department of Surgery and *Department of Radiology, Royal Infirmary, Glasgow, UK*
Correspondence to: Mr J R. Anderson, Southern General Hospital, 1345 Govan Road, Glasgow G51 4TF, UK

A total of 103 consecutive patients with gastric adenocarcinoma was assessed for intra-abdominal spread of malignancy using ultrasonography, computed tomography (CT) and laparoscopy under general anaesthesia. Histologically proven metastases were to the liver in 27 patients, lymph nodes in 49 and directly to peritoneum in 13. All modalities showed a high specificity (92–100 per cent) for each type of metastasis. Laparoscopy was more sensitive in detecting hepatic, nodal and peritoneal metastases; the relative performance of laparoscopy was best with regard to hepatic metastases. Ultrasonography and CT were particularly poor at detecting nodal and peritoneal metastases. There was no significant morbidity and no mortality associated with laparoscopy, which was more accurate in preoperative staging of gastric cancer than ultrasonography or CT.

Despite a declining incidence, gastric cancer remains the fourth most common malignant tumour in the UK, causing 11 000 deaths per year[1]. Preoperative staging for spread of the disease is routinely performed in most centres using ultrasonography and computed tomography (CT). Staging of gastric cancer guides the clinician regarding prognosis, assists in operative planning and may prevent unnecessary laparotomy in selected patients for whom non-operative therapies are now available. CT and ultrasonography both have limitations in staging gastric cancer. CT achieves accuracy rates of 29–72 per cent for the detection of hepatic metastases in recently reported series[2–7], with most authors agreeing that it is not reliable for staging the disease without other investigations. Laparoscopy is of proven benefit in the staging of oesophageal cancer[8]. The aim of this study was to compare the accuracy of ultrasonography, CT and laparoscopy in the staging of patients with gastric adenocarcinoma.

Patients and methods

Between 1988 and 1991, 103 consecutive patients with biopsy-proven gastric adenocarcinoma were assessed. All carcinomas were included except tumours localized to the cardia, which have previously been studied[8]. Patients with gastric lymphoma were excluded. Ultrasonography was performed using an Advanced Technology Laboratories (Washington, UK) real-time ultrasound scanner fitted with a 3.5-MHz transducer and contrast-enhanced CT using a GE model 9800 Hilight whole-body scanner (GEC, Milwaukee, Wisconsin, USA). Laparoscopy was performed under general anaesthesia with intermittent positive-pressure ventilation as a separate staging procedure. An Olympus (Keymed, Southend, UK) 30° oblique viewing laparoscope was used with an Eder Insumat carbon dioxide Insufflator (Down Surgical, Mitcham, UK). The laparoscope was usually inserted subumbilically, and, when indicated, a liver sample biopsy was obtained using a Tru-Cut (Travenol Laboratories, Deerfield, Illinois, USA) biopsy needle. Intra-abdominal metastases were considered to be proven only when histological confirmation was available Nodal and peritoneal metastases therefore required laparotomy to obtain material for histological examination. Hepatic metastases were biopsied percutaneously under direct vision. All investigations were carried out by experienced personnel, who were unaware of the results of previous investigations. The sensitivity, specificity and accuracy of each technique were calculated and the results compared using an uncorrected χ^2 test. The sensitivity of an investigation is the proportion of positive tests in all patients with proven disease, the specificity is the proportion of negative tests in all patients proven to be disease-free, and the accuracy is the ratio of correct results (true positive and true negative) to the total number of tests.

Results

There were 68 men and 35 women aged between 33 and 91 years, with a mean age of 65 years. The distribution of tumours is shown in *Table 1*. Of the 103 patients, 22 had biopsy-proven hepatic metastases at laparoscopy and were treated without surgery (four with hepatic metastases at laparoscopy proceeded to laparotomy and one with a negative laparoscopy was found to have hepatic metastases at laparotomy). A further 16 patients were also treated conservatively: ten had obvious peritoneal metastases at laparoscopy, three had advanced nodal disease and were medically unfit, two declined surgery despite being free from metastases at staging and one had pulmonary metastases detected radiologically. These 16 patients are excluded from the study as the findings at staging could not be confirmed surgically. The remaining 65 patients proceeded to laparotomy.

Of the 38 patients treated without surgery, 31 had laser therapy to control local disease, five had pulsion intubation, one had chemotherapy alone and one had no treatment. In this group, there were 11 patients with hepatic metastases and ten with peritoneal metastases, which were detected only by laparoscopy.

Table 1 Distribution of gastric tumours

	No. of tumours
Proximal third of stomach	60
Body of stomach	24
Antrum	10
Body and antrum	6
Fundus	2
Linitis plastica	1

Presented to the Surgical Research Society in Glasgow, UK, July 1994
Paper accepted 10 October 1995

Fifty-three of the 65 patients treated surgically had resection of the primary tumour. Of the remaining 12 patients with unresectable local disease, five had operative intubation, three had laser therapy, two had chemotherapy, one had a palliative gastrojejunostomy, and one had a laparotomy and died before further treatment. All patients undergoing laparotomy had biopsy of peritoneal deposits and sampling from all accessible nodal areas.

Twenty-seven patients had histologically confirmed liver metastases either at laparotomy and biopsy ($n = 1$) or by laparoscopy and percutaneous biopsy ($n = 26$). Forty-nine of the 65 patients undergoing surgery had histologically proven nodal metastases, and 13 had proven peritoneal deposits. Of the 65 patients undergoing surgery, only 16 had the disease confined to the stomach.

Laparoscopy was significantly more sensitive than other modalities in the detection of liver metastases. Of the 27 patients with histologically proven liver metastases, 26 were correctly identified by laparoscopy, compared with ten by ultrasonography and 14 by CT (*Table 2*). The one false negative reported by laparoscopy was in a patient who had two small posterior hepatic metastases, one in the right and one in the left lobe. These lesions were also missed by ultrasonography and CT.

Table 2 Comparison of indices for hepatic metastases in the staging of gastric adenocarcinoma by three modalities*

	Laparoscopy	Ultrasonography	CT
True positive	26	10	14
Sensitivity (%)	96	37	52
True negative	60	57	55
Specificity (%)	100	95	92
False positive	0	3	5
False negative	1	17	13
Accuracy (%)	99	76	79

*Hepatic metastases were histologically proven in 27 patients and confirmed absent in 60.
Sensitivity: laparoscopy *versus* ultrasonography $\chi^2 = 21{\cdot}33$, 1 d.f., $P < 0{\cdot}001$; laparoscopy *versus* CT $\chi^2 = 13{\cdot}89$, 1 d.f., $P < 0{\cdot}001$. Specificity: laparoscopy *versus* ultrasonography $\chi^2 = 3{\cdot}08$, 1 d.f., $P < 0{\cdot}1$; laparoscopy *versus* CT $\chi^2 = 5{\cdot}22$, 1 d.f., $P < 0{\cdot}05$. Accuracy: laparoscopy *versus* ultrasonography $\chi^2 = 18{\cdot}43$, 1 d.f., $P < 0{\cdot}001$; laparoscopy *versus* CT $\chi^2 = 16{\cdot}1$, 1 d.f., $P < 0{\cdot}001$. CT, computed tomography

Table 3 Comparison of indices for nodal metastases in the staging of gastric adenocarcinoma by three modalities*

	Laparoscopy	Ultrasonography	CT
True positive	26	6	13
Sensitivity (%)	53	12	27
True negative	16	16	16
Specificity (%)	100	100	100
False positive	0	0	0
False negative	23	43	36
Accuracy (%)	65	34	45

*Nodal metastases were histologically proven in 49 patients and confirmed absent in 16. Sensitivity: laparoscopy *versus* ultrasonography $\chi^2 = 18{\cdot}56$, 1 d.f., $P < 0{\cdot}001$; laparoscopy *versus* CT $\chi^2 = 7{\cdot}19$, 1 d.f., $P < 0{\cdot}01$. Accuracy: laparoscopy *versus* ultrasonography $\chi^2 = 12{\cdot}31$, 1 d.f., $P < 0{\cdot}001$; laparoscopy *versus* CT $\chi^2 = 5{\cdot}24$, 1 d.f., $P < 0{\cdot}05$. CT, computed tomography

Table 4 Comparison of indices for peritoneal metastases in the staging of gastric adenocarcinoma by three modalities*

	Laparoscopy	Ultrasonography	CT
True positive	9	3	1
Sensitivity (%)	69	23	8
True negative	52	52	52
Specificity (%)	100	100	100
False positive	0	0	0
False negative	4	10	12
Accuracy (%)	94	84	81

*Peritoneal metastases were histologically proven in 13 patients and absent at laparotomy in 52. Sensitivity: laparoscopy *versus* ultrasonography $\chi^2 = 5{\cdot}57$, 1 d.f., $P < 0{\cdot}05$; laparoscopy *versus* CT $\chi^2 = 10{\cdot}40$, 1 d.f., $P < 0{\cdot}1$. Accuracy: laparoscopy *versus* ultrasonography $\chi^2 = 2{\cdot}88$, 1 d.f., $P < 0{\cdot}1$; laparoscopy *versus* CT $\chi^2 = 4{\cdot}56$, 1 d.f., $P < 0{\cdot}05$. CT, computed tomography

Of the 27 patients with hepatic metastases, nine were identified by all three modalities, five by laparoscopy and CT alone, one by laparoscopy and ultrasonography alone, and 11 by laparoscopy alone. Laparoscopy did not achieve the same sensitivity with regard to nodal metastases, detecting only 26 of the 49 histologically proven cases compared with six by ultrasonography and 13 by CT (*Table 3*).

Of the 13 patients with histologically proven peritoneal metastases, nine were detected by laparoscopy compared with three by ultrasonography and one by CT (*Table 4*). All three patients correctly identified by ultrasonography had ascites from which the presence of peritoneal metastases was inferred. The four false-negative results reported by laparoscopy included one metastatic deposit in the transverse mesocolon, one deposit on the posterior surface of the greater omentum and one deposit lying on the pancreas. One diaphragmatic peritoneal metastasis was also missed at laparoscopy.

Discussion

The present series of 103 patients shows a majority of proximal third lesions compared with those of the distal third. This may reflect referral bias in the authors' unit which has an interest in the management of dysphagia, but is in keeping with observed recent trends[9]. The value of preoperative staging for these patients lies in identifying those who will not benefit from resectional or bypass surgery. This is becoming of increasing importance with the advent of non-operative means of tumour palliation: chemotherapy, laser therapy and intubation. None of the patients in the study who underwent palliative therapy required surgery before death. Despite these treatment methods, however, some patients with metastases demonstrated by staging will require palliative surgery, particularly those with lesions of the antrum causing gastric outlet obstruction.

The detection of nodal metastases is of lesser importance than hepatic metastases as their presence does not always preclude surgical resection of the tumour; indeed laparoscopy is unlikely to detect small nodal deposits or nodal disease around the coeliac axis. Laparoscopy as used in this series had limitations in the detection of peritoneal metastases as a single viewing port was used without the aid of dissecting or manipulating instruments. For this reason, deposits concealed by the stomach, omentum or mesentery were not accessible. The development of improved laparoscopic techniques now enables dissection and biopsy for histological confirmation to be performed with ease. Ultrasonography and CT are able only to suggest the presence of peritoneal metastases by the detection of ascites, and the difference between the two modalities in the present study probably reflects interobserver variation.

However, all three modalities were highly specific; laparoscopy achieved significantly higher specificity than CT only in the detection of hepatic metastases ($\chi^2 = 5{\cdot}22$, 1 d.f., $P < 0{\cdot}05$). This is reflected in the accuracy rates which are also high for all three modalities, although laparoscopy is significantly more accurate than other modalities except in comparison with that of ultrasonography in the detection of peritoneal metastases.

Another benefit of performing laparoscopy as a separate staging procedure is that it allows an assessment of the patient's ability to tolerate anaesthesia and surgical trauma before embarking on resectional surgery.

The 1987 Union Internacional Contra la Cancrum classification of gastric cancer categorizes tumour spread according to the tumour node metastasis (TNM) system. Laparoscopy is of particular value in assessing metastases distant from the primary tumour site (M stage). It also provides the opportunity to biopsy under vision suspected hepatic metastases, thereby avoiding the ambiguity often associated with radiological investigation. Laparoscopy tends to understage nodal disease, particularly retrogastric involvement, and provides little information about depth of tumour invasion unless the serosa is breached. Endoscopic ultrasonography is proving increasingly accurate at staging T and N disease[10,11]. Laparoscopic ultrasonography may increase the detection of lymphadenopathy; however, as this does not prove the presence of metastatic disease, it is unlikely to reduce the need for laparotomy. In the present study the 'gold standard' for comparing the accuracy of the different modalities is taken as being the findings at laparotomy and tissue sampling. The results show that all modalities underestimate the extent of disease. More recent methods of detecting microscopic or 'occult' metastases such as intraoperative ultrasonography or hepatic perfusion studies have not yet been fully assessed in gastric cancer.

Published work gives conflicting opinions on the value of laparoscopy in staging gastric cancer. In an early work Possik *et al.*[12] evaluated 360 patients and attained a sensitivity of 87·2 per cent for laparoscopy in the detection of hepatic metastases, concluding that it is a superior diagnostic method than radiological tests. Kriplani and Kapur[13] attained an accuracy of 91·6 per cent in the detection of hepatic metastases in a series of 40 patients and Forse and colleagues[14] demonstrated the benefit of laparoscopy in reducing the hospital stay of patients with an unresectable tumour.

Despite this work, laparoscopy has not gained popularity in the staging of gastric cancer. In a large multicentre study published by the German Gastric Cancer TNM Study Group in 1989[15] diagnostic laparoscopy was dismissed as being 'of limited clinical utility' in the staging of gastric cancer. Some 37 per cent of the present series did not undergo surgery as a result of findings at staging and laparoscopy had the major role in identifying this group.

Laparoscopy offers a safe, sensitive and specific method of staging patients with gastric carcinoma. This is of increasing importance in planning patient management with the use of non-operative methods of tumour palliation.

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British Journal of Surgery 1996, 83, 1263–1267

Functional and morphological study of the cricopharyngeal muscle in patients with Zenker's diverticulum

G. ZANINOTTO, M. COSTANTINI, C. BOCCÙ, M. ANSELMINO, A. PARENTI*, D. GUIDOLIN† and E. ANCONA

*Departments of Surgery and *Pathology, University of Padova School of Medicine, and †Fidia Research Laboratories, Abano Terme, Padova, Italy*

Correspondence to: Professor G. Zaninotto, Department of Surgery, University of Padova, Via Giustiniani 2, 35128 Padova, Italy

Pharyngo-oesophageal function was investigated in 12 patients with Zenker's diverticulum before and after cricopharyngeal myotomy with or without diverticulectomy using low-compliance, high-frequency oesophageal manometry. Nine healthy volunteers served as controls. The amount of muscle and connective tissue in the cricopharyngeal muscle was also measured by computerized morphometry and compared with findings in cadavers with no history of dysphagia. Preoperative manometry in patients with Zenker's diverticulum showed an incomplete relaxation of the upper oesophageal sphincter (UOS) (the residual UOS pressure at swallowing was 7·9 (range 1–20) mmHg in patients *versus* 0·2 (−12·5–14) mmHg in controls; $P<0·001$) and increased pharyngeal intrabolus pressure (21 (range 0–52) *versus* 9 (range 0–16) mmHg; $P<0·01$), with no pharyngo-oesophageal coordination abnormalities. Both parameters significantly decreased after myotomy. Patients with Zenker's diverticulum had significantly fewer muscle fibres in the cricopharyngeus and the muscle:connective tissue ratio was significantly lower (0·94 (range 0·8–1·4) in patients *versus* 1·5 (1·4–3·6) in controls; $P<0·05$). This study supports the theory that Zenker's diverticulum is caused by an increased intrapharyngeal pressure at swallowing due to incomplete cricopharyngeal muscle relaxation resulting from localized sclerosis.

The role of disordered cricopharyngeal muscle function in the pathogenesis of pharyngeal pouches – or so-called Zenker's diverticula – remains unclear. There is equally no agreement as to the role of cricopharyngeal myotomy in their treatment. This study was therefore undertaken to study cricopharyngeal muscle function (as evaluated by manometry) and morphology in a group of 12 consecutive patients with Zenker's diverticulum, and to evaluate changes induced by myotomy and diverticulectomy in pharyngo-oesophageal function.

Patients and methods

Between January 1991 and May 1995, 12 patients (four women and eight men of median age 65 (range 43–79) years) were referred with symptoms related to Zenker's diverticulum. They all complained of dysphagia, described as a sense of food sticking in the throat, and this was defined as severe (interfering with normal activity) in five and moderate in seven. Regurgitation of food was reported in ten and aspiration (nocturnal coughing, wheezing and/or recurrent pneumonia) occurred in seven. Dysphagia and regurgitation were scored according to intensity (1 = mild, not reported spontaneously by the patient; 2 = moderate, reported spontaneously but not interfering with normal activity; and 3 = interfering with normal activity) and frequency (1 = occasionally; 2 = once a week; 3 = twice or three times a week; and 4 = daily). Aspiration symptoms were scored as present (1) or absent (0). The sum of the scores for the single symptoms was considered as the patient's symptom score. The median duration of symptoms was 12 (range 2–48) months

The diagnosis of Zenker's diverticulum was usually obtained with a barium swallow. The diverticula measured (in their longest axis) less than 2 cm in three patients, between 2 and 4 cm in seven and more than 4 cm in two. All patients underwent oesophageal manometry and upper gastrointestinal endoscopy to exclude any concomitant abnormalities of the oesophagus and stomach. In the event of the diverticulum interfering with its placement, the manometric probe was passed with the aid of a guidewire positioned at endoscopy.

Nine healthy volunteers (seven men and two women of median age 38 (range 24–80) years) served as a control group.

Manometric evaluation

Manometry was performed with the instruments and technique described in detail elsewhere[1]. Briefly, an eight-lumen low-compliance infused system with computerized data acquisition and analysis was employed. A high-frequency data acquisition mode (50 Hz) was used in view of the rapidity of events occurring during swallowing. Upper oesophageal sphincter (UOS) pressure was measured while the catheter was withdrawn at a constant rate of 5 mm/s. The maximum amplitude registered by each probe during its passage through the UOS was averaged and considered as the UOS pressure. To evaluate the pharyngo-oesophageal segment, the manometric probe with four radially orientated side holes was positioned at the upper edge of the UOS, with two other side holes situated 5 and 10 cm above (in the distal and proximal pharynx respectively) and one 5 cm below (in the cervical oesophagus). Five swallows of 5 ml water were evaluated. The following parameters of pharyngeal contractions were considered: amplitude, duration and intrabolus pressure, i.e. the pressure generated by the passage of the bolus in the distal pharynx and seen at manometry as a slow pressure increase (shoulder) before the major upstroke generated by contractions of the pharyngeal wall, as described by Cook *et al.*[2] (*Fig. 1*), UOS relaxation (expressed as the residual pressure at swallowing) and the coordination of UOS opening with pharyngeal contractions, as described by Knuff *et al.*[3].

Operation

A left laterocervical approach, anteromedial to the sternocleidomastoid muscle, was used. All the diverticula were excised and, if 2 cm or greater in size, transected with a stapler. Small diverticula were left in place in three patients. The cricopharyngeal muscle fibres were divided in the midline

Paper accepted 20 November 1995

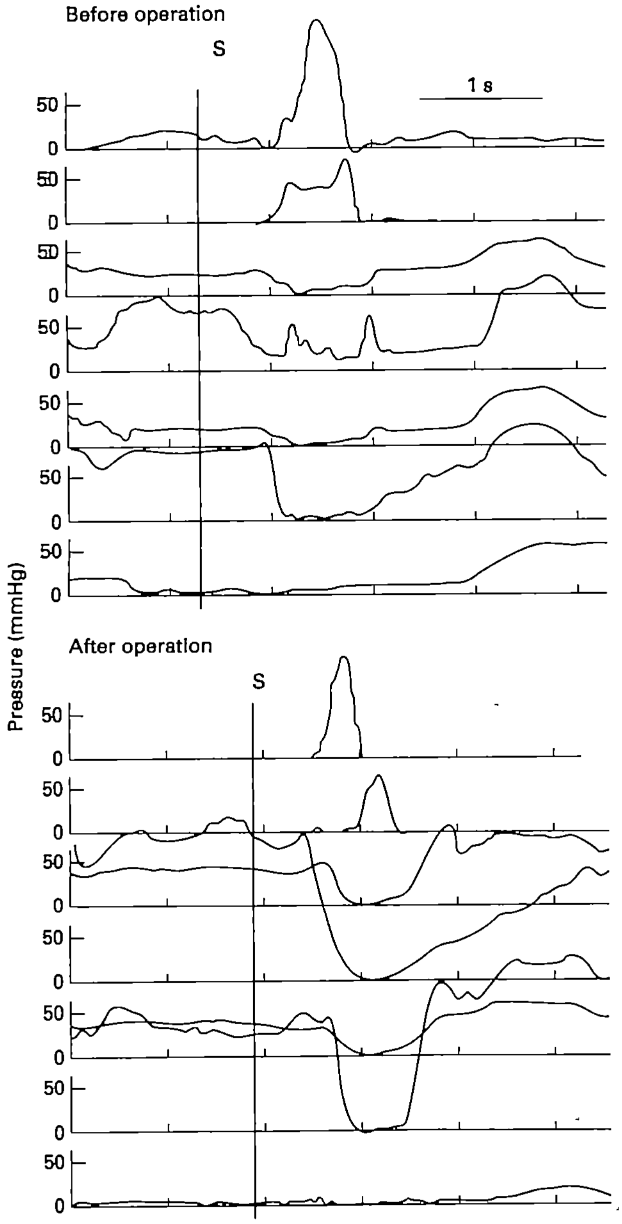

Fig. 1 Pharyngo-oesophageal manometry in a patient with Zenker's diverticulum before (above) and after (below) diverticulectomy and myotomy. The manometric probes are positioned in the proximal pharynx (upper trace), in the distal pharynx (second trace), at the upper edge of the upper oesophageal sphincter (UOS), 90° apart (the four central traces) and in the proximal oesophagus (lower trace) 5 cm below the upper edge of the UOS. The fourth probe is directed towards the right lateral wall of the UOS and an incomplete relaxation of the UOS is detected only by this probe, probably because of the UOS asymmetry. The sensor immediately above (in the distal pharynx) records a slow increase in pressure (intrabolus pressure) immediately before the major upstroke, indicating a slow passage of the bolus through the sphincter because of reduced compliance or incomplete relaxation. Both findings are no longer evident after surgery. The vertical lines (S) mark the swallows

posteriorly from the neck of the sac down to the oesophagus for 4–5 cm. Specimens of cricopharyngeal muscle were collected in seven patients. A Nissen fundoplication was also performed in one patient with gastro-oesophageal reflux and hiatus hernia.

Histological and morphometric studies

The muscle biopsy specimens were fixed in 10 per cent buffered formalin. Morphometry was performed on Masson's trichrome-stained sections, using a computerized image analysis system (AT-IBAS, Kontron, Eching, Germany), connected through a black and white television camera (Bosch TYK9B) to an optical microscope (UMSP80, Zeiss, Oberkochen, Germany). Sections were sampled field by field and two images for each field were stored using a monochromatic light of 400 and 450 nm respectively. After correction for uneven illumination and contrast enhancement, the areas occupied by connective tissue or muscle fibres were distinguished by means of a suitable threshold and the area fractions were measured. The grey threshold was maintained constant for the whole measurement. Three sections for each sample were examined and the values obtained were averaged.

Five specimens of cricopharyngeal muscle collected from sex- and age-matched cadavers with no history of dysphagia or presence of diverticulum at post-mortem examination served as a control group.

Statistical analysis

Findings were stored in a database (DB3, Ashton Tate, USA) and analysed using a commercially available statistical package (Statgraphics, STSC Plus Ware Product, USA). The Wilcoxon and Mann–Whitney *U* tests were used, as appropriate. Values are expressed as median (range).

Results

Surgical outcome

One patient had a leak which was treated conservatively, maintaining the patient on enteral nutrition via nasogastric tube for 10 days. The median follow-up was 5 (range 3–35) months and all but two patients were asymptomatic; two complained of occasional moderate dysphagia. The symptom scores before and after surgery are shown in *Fig. 2*.

Manometric findings

Patients with Zenker's diverticulum had increased intrabolus pressure in pharyngeal contractions and an increased residual UOS pressure at swallowing (*Fig. 3*). Their resting UOS pressure was lower, though not significantly so, than in controls. No differences were observed in pharyngo-oesophageal coordination, duration of UOS opening, or amplitude and duration of pharyngeal contractions (*Table 1*).

A statistically significant reduction in intrabolus pressure, minimal UOS pressure at swallowing and resting UOS pressure was observed in the nine patients who agreed to undergo a repeat manometric test a median of 3 (range 1–35) months after operation (*Fig. 4*).

Histological and morphometric studies

Histological examination of the seven specimens showed a marked decrease in the amount of muscle fibre in the cricopharyngeus. The muscle:connective tissue ratio was consequently significantly lower in patients than in controls (*Fig. 5*).

Discussion

Since the first case of pharyngo-oesophageal pouch was described by Ludlow in 1764[4], many theories have been

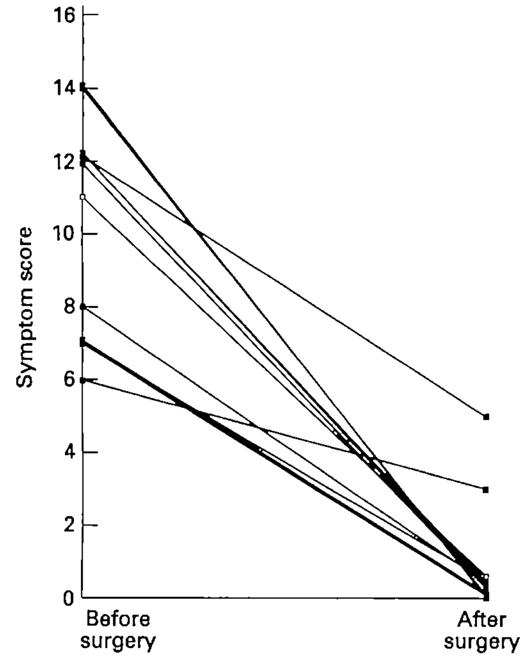

Fig. 2 Symptom scores for each patient before and after surgery. Two patients still had moderate dysphagia after treatment

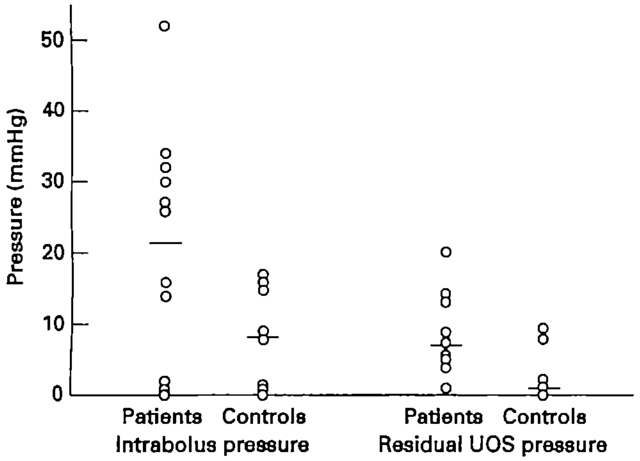

Fig. 3 Intrabolus pressures (left) and residual upper oesophageal sphincter (UOS) pressures at swallowing (right) in patients and controls. Both measurements differ significantly ($P<0{\cdot}01$ and 0·001 respectively, Mann-Whitney *U* test)

Table 1 Pharyngosphincteral manometric parameters in patients with Zenker's diverticulum

	Patients	Controls
Pharyngeal contractions		
Amplitude (mmHg)	68·0 (27–105)	34·5 (10·3–62)
Duration (s)	0·7 (0·5–1·0)	0·9 (0·1–1·0)
UOS		
Resting pressure (mmHg)	35·0 (24–60)	57·8 (25·7–90)
Duration of relaxation (s)	1·3 (0·8–1·9)	1·0 (0·8–1·3)
Time difference between pharyngeal peak and maximum UOS relaxation (s)	0·2 (0·6–0·1)	0·3 (1·1–0·1)

Values are median (range). UOS, upper oesophageal sphincter

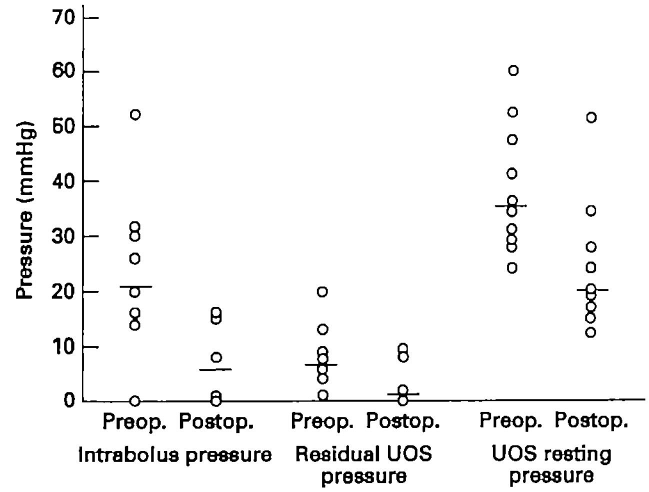

Fig. 4 Preoperative and postoperative manometric readings of the pharynx and oesophagus in nine patients with Zenker's diverticulum. The intrabolus pressure decreased from 21 to 8 mmHg; the residual upper oesophageal sphincter (UOS) pressure at swallowing decreased from 7·9 to 1·8 mmHg; and the UOS resting pressure decreased from 35 to 20 mmHg. All three measurements were statistically significant ($P<0{\cdot}05$, Wilcoxon test)

postulated to explain its aetiology. Zenker and Von Ziemssen[5] proposed that herniation of the pouch proximal to the cricopharyngeal muscle might be caused by high pharyngeal pressures, the actual site of herniation being determined by a zone of weakness in the posterior wall – the so-called Killian's dehiscence. The suggestion that the cricopharyngeal muscle might be involved in the development of Zenker's diverticulum arose initially from endoscopic and radiographic studies describing premature contractions of the cricopharyngeus and failure to achieve relaxation (achalasia of the UOS)[6,7]. When pharyngo-oesophageal function was investigated by manometry, however, the findings were inconsistent. In the early 1980s, attention focused on delayed UOS opening in relation to pharyngeal contraction and a lack of UOS coordination became the most widely accepted assumed cause of Zenker's diverticulum[8,9]. Manometric tests failed to detect any abnormality in 40–60 per cent of patients with Zenker's diverticulum, however, and this theory was further undermined by subsequent research: Knuff, for example, observed no manometric abnormality in nine patients with Zenker's diverticulum.

There are several reasons why manometric testing may fail to detect pharyngo-oesophageal function abnormalities in Zenker's diverticulum: the cricopharyngeal muscle, which roughly corresponds to the UOS, generates asymmetric pressures with a considerable variability in each of the axes[10]; contractions of the pharyngeal striated muscle cause pressure events to be much faster and greater in amplitude than in the distal oesophagus[11]; moreover, the UOS is extremely mobile and moves proximally nearly 1 cm during swallowing, thus causing the recording site to 'drop out' if it is placed in the central part of the UOS. This 'dropping out' of the recording site may explain the apparently 'normal' relaxation observed by previous researchers.

Manometric study of the pharyngo-oesophageal complex calls for a careful method and suitable technology: to

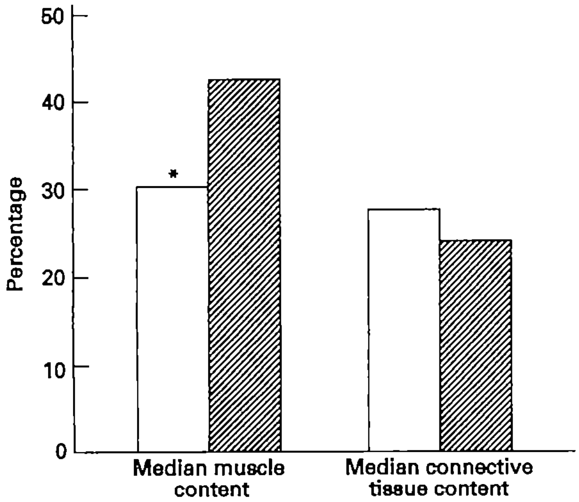

Fig. 5 Median content of muscle (left) and connective tissue (right) in the cricopharyngeal muscle of patients with Zenker's diverticulum (□) and cadaveric specimens of subjects without dysphagia (▨). Muscle: 30·1 per cent in patients *versus* 42·6 per cent in controls ($^*P < 0·05$, Mann-Whitney U test); connective tissue: 27·4 per cent in patients *versus* 23·9 per cent in controls

overcome the asymmetry, four side holes at the same level were used in the UOS; higher frequency sampling was used to detect the faster events in the pharynx and the four side holes were carefully positioned at the upper margin of the UOS to avoid any 'drop-out' phenomena. Although optimal recording of pharyngeal contractions can be achieved only by solid-state catheter, the present study was not intended to measure maximum intrapharyngeal pressures. The perfused side holes certainly underestimate the maximum pressure, but they none the less detect intrabolus pressures with a low rate of increase, which were measured well within the capability of the system. The authors' method was very similar to the one described by Cook *et al.*[2] (except for sleeve probes into the UOS rather than side holes) and very similar results were obtained. The main abnormality detected in patients with Zenker's diverticulum was a failure to achieve complete relaxation and a consequent increase in pharyngeal intrabolus pressure during the phase of trans-sphincter bolus flow. This manometric finding is probably related to a primary cricopharyngeal muscle dysfunction. In fact, the finding of a normal duration and coordination of UOS opening suggests that the disorder is caused by a diminished sphincter compliance rather than by pharyngeal incoordination. The observation by Cook and colleagues[2] that hyoid motion is normal in extent and timing in patients with Zenker's diverticulum also supports a localized mechanical disturbance rather than a lack of neuromuscular coordination.

Cricopharyngeal muscle alterations have been reported: Lerut *et al.*[12] observed a weaker contraction curve with a lower amplitude, a longer time to peak twitch and a much longer muscle fibre relaxation time in an '*in vitro* study' on patients with Zenker's diverticulum. The muscle fibres also showed a reduction in their content of acetylcholinesterase, a predominant distribution of type I muscle fibres and an increase in fibrotic tissue. The results of the present study confirm and objectively measure the reduction in muscle fibres in the cricopharyngeal muscle. This probably causes the reduced compliance and contractility of the muscle. The aetiology of this relative fibrosis is not known. Lerut and co-workers[12] took biopsy samples from the sternocleidomastoid muscle of patients with Zenker's diverticulum and found no abnormalities, thus excluding the presence of any generalized myopathy. Whether these morphological and functional changes are primary causal factors in the genesis of Zenker's diverticulum, or merely secondary to the compression caused by the diverticulum itself, remains to be seen. However, the reduction in muscle component was found in smaller Zenker's diverticula as well as in larger ones, and it is hardly likely that a 2-cm pouch could cause sufficient compression on the cricopharyngeal muscle to give rise to such changes.

Cricopharyngeal myotomy in association with diverticulectomy or diverticulopexy has gained in popularity in the past 20 years and has been widely used, despite the lack of manometric evidence of any cricopharyngeal muscle function impairment in Zenker's diverticulum[13]. The reason for adding a myotomy was mainly based on the observation of a lower complication rate when myotomy was added, as reported in a survey carried out in the Group Européen d'Etude des Maladies de l'Oesophage[14]. This strictly empirical experience seems to confirm the role of the cricopharyngeal muscle in symptoms of Zenker's diverticulum, justifying myotomy as an essential step in its treatment.

The effect of myotomy was evident in the present patients, with a decrease in UOS resting pressure and residual UOS pressure at swallowing, and a reduction in pharyngeal intrabolus pressure. The relief from dysphagia (which cannot be explained by the diverticulectomy alone, as an improvement in symptoms was also obtained in patients with small diverticula left untouched) is probably related to the improved relaxation of the UOS due to the myotomy. This being so, a much higher incidence of recurrence would be expected if myotomy was not performed – but this is not the case, possibly because recurrence might take a long time to develop and, as patients with Zenker's diverticulum are elderly, most will die before any recurrence becomes apparent.

In conclusion, this study confirms the old Zenker and Von Ziemssen[5] hypothesis of an increased intrapharyngeal pressure in the pathogenesis of pharyngeal pouches and of the central role played by the cricopharyngeal muscle. The reduction in cricopharyngeal muscle compliance is probably related to the reduction in muscle fibres and qualitative alterations of the fibres. Cricopharyngeal myotomy is therefore an essential part of the treatment of Zenker's diverticulum.

Acknowledgements

This research was funded by the Italian National Research Council (C.N.R.) grant no. 94.02522.CT04.

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British Journal of Surgery 1996, 83, 1268–1270

Anatomy of the extrinsic motor nerve supply to mobilized segments of the oesophagus disrupted by dissection during repair of oesophageal atresia with distal fistula

M. R. Q. DAVIES

Division of Paediatric Surgery, University of the Witwatersrand Medical School, Johannesburg, South Africa
Correspondence to: Professor M. R. Q. Davies, Division of Paediatric Surgery, 154/28 Johannesburg Hospital, Private Bag X39, Johannesburg 2000, South Africa

Atresia of the oesophagus occurs near to the site of convergence of the foregut with structures of branchial arch origin. This is a confluence of a striated muscle tube with a somatic nerve supply and a smooth muscle tube with an autonomic nerve supply. The implications, with regard to function, of denervating the oesophagus during operation are influenced by this anatomy. During dissection of a cadaver with oesophageal atresia and distal fistula, the sites of potential nerve injury were displayed. Damage to these nerves occurs during routine primary repair and may contribute to oesophageal motor dysfunction after successful surgery.

Patients who have had an oesophageal atresia with distal fistula repaired seldom complain about their ability to swallow even though they have significant functional abnormality which can be confirmed by manometric evaluation[1,2]. Never having experienced normal function, symptoms that would be incapacitating for many remain unrecognized.

The anatomy of the vagus nerve, the extrinsic motor supply to the oesophagus and stomach, has surgical importance and little attention has been given to the branches that supply the pharynx and oesophagus. The possibility of disruption of this supply during repair of an oesophageal atresia has not been addressed previously, although nerve damage to the mobilized segments is known to occur[3–5].

A cadaveric dissection performed to illustrate the site of nerve disruption during primary repair of an oesophageal atresia of the common type is described.

Methods

The extrinsic motor nerve supply to the proximal and distal segments of an unrepaired oesophageal atresia with distal tracheo-oesophageal fistula was identified by dissection. The oesophageal pouch and fistula segments were mobilized surgically, and nerve damage was noted and photographed (*Figs 1–3*). Attention is drawn to the fact that the recurrent nerves and their branches were dissected and released from surrounding tethering structures in the illustrations. This allowed the nerves to be identified clearly.

Results

An extensive plexus of nerves surrounds the oesophagus immediately distal to the tracheo-oesophageal fistula. The right vagus and its branches form its proximal part but it is soon joined by major contributions from the left vagus nerve.

The proximal portion of the oesophagus distal to the tracheo-oesophageal fistula could easily be mobilized within this plexus, but small direct branches to the oesophagus were divided during dissection.

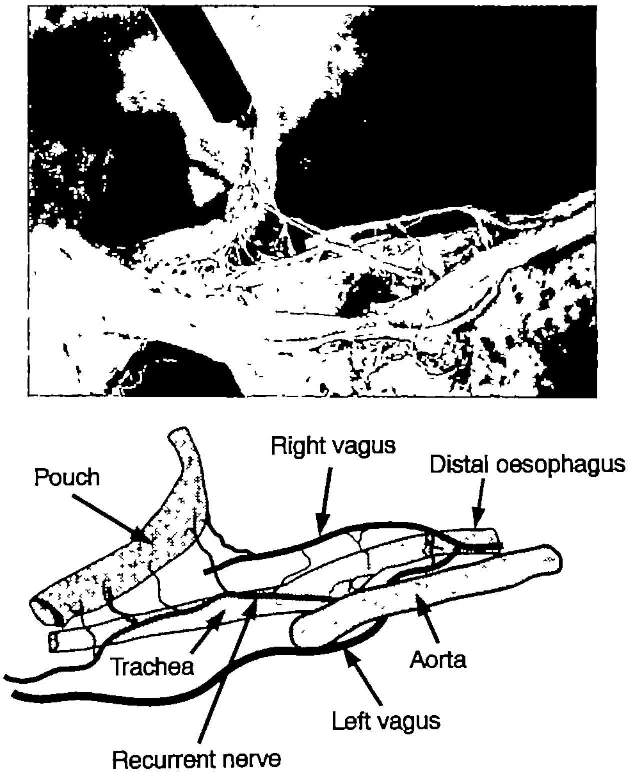

Fig. 1 Left vagus and left recurrent laryngeal nerve. The specimen is in the prone position, with the craniad end to the left. The tip of the atretic oesophagus has been transfixed by a probe. The distal part of this structure was dissected free from all tethering fibres and nerves. Uncut nerves to the pouch are shown. Note the segmental nature of this supply. The right vagus and its branches have been lifted off the proximal end of the distal oesophagus. The left recurrent laryngeal nerve arises from the vagus as this nerve passes in front of the aorta

In the presence of oesophageal discontinuity, a plexus of nerves lies on the trachea immediately distal to the atresia. These nerves have their origin from the right vagus and left recurrent laryngeal nerves. This plexus was damaged during dissection of the proximal pouch. As this structure was lifted off and mobilized from the trachea, its

Paper accepted 10 December 1995

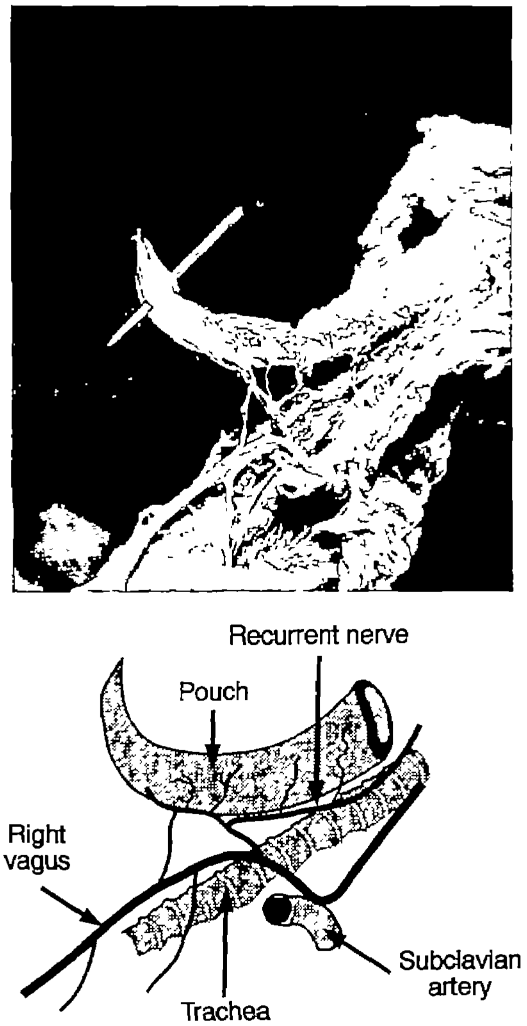

Fig. 2 Right vagus and right recurrent laryngeal nerve. The specimen is shown obliquely from the back with its craniad end to the right. The course of the right vagus nerve is shown; it has been misplaced to lie behind, instead of in front of, the cut end of the subclavian artery, the site of origin of recurrent laryngeal nerve. The atretic end of the mobilized oesophagus is held up by the probe. The nerve supply that it receives from the recurrent nerve is shown

segmental nerve supply, branches from the right and left recurrent laryngeal nerves, were divided.

Discussion

Deglutition occurs as a result of muscle contraction which involves a coordinated primary wave. It differs from peristaltic activity in other parts of the intestine in that the initial step is voluntary and involves striated muscles. Pharyngo-oesophageal contraction occurs without interruption to the wave of movement.

The vagus is the motor nerve to the oesophagus. In oesophageal atresia with distal fistula it has been shown that the atresia occurs at an anatomical watershed[6]. The proximal oesophageal pouch has striated muscles in its wall; the distal oesophagus has none. The central nerve stations for the nerve fibres that supply these muscles are different. Outside the brainstem the vagus nerves become confluent with the cranial roots of the accessory nerves. These fibres are found in the recurrent laryngeal nerves which supply the striated muscles of the pharynx and proximal oesophagus. They have their central origin in the nucleus ambiguus of the medulla oblongata. The remainder of the oesophagus is supplied by vagus nerve fibres which have their origin in the dorsal nucleus of the vagus. The transition from a striated to a smooth muscle tube does not occur abruptly. Histological evaluation established that, the tip of the pouch in the cadaver investigated contained striated muscle. In the event of the primary peristaltic wave emptying the oesophagus incompletely, a new and locally generated wave of contraction occurs. This contraction, induced by mural stretch receptors, is under the control of the intrinsic nerve supply of the oesophagus and is found only in the smooth muscle section. A single secondary peristaltic wave normally empties the oesophagus.

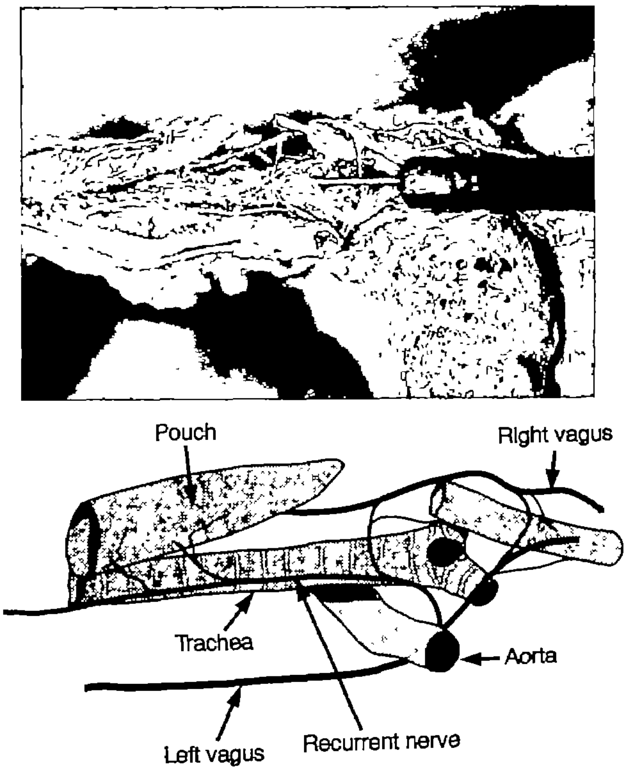

Fig. 3 Tracheo-oesophageal fistula. The specimen is in the prone position with the craniad end to the left. The tracheo-oesophageal fistula has been dissected free from the trachea at its bifurcation. Probes in the lumen of the oesophagus and the trachea mark the site of amputation. The relationship of the right vagus to this part of the distal oesophagus is shown as well as communicating branches between it and the left recurrent nerve and its parent nerve, the vagus

Since the first successful surgical repairs of oesophageal atresia were reported, abnormal swallowing has been documented[1,2,7,8]. When this occurs in patients in whom the operation was technically successful, it is attributed to a congenital cause. Abnormalities of the intrinsic nerve plexus have been reported[9] but the prevalence and role played by a congenital deficiency in postoperative dysphagia is not clear[10]. In a recent study which compared oesophageal peristaltic activity before and after surgery for atresia it was concluded that the motor abnormality resulted directly from the surgery[11]. The findings of the present study partially support this statement. During mobilization of the proximal oesophageal pouch it was shown that most of its extrinsic nerve supply was interrupted, the devastating consequences of which are well known. Oropharyngeal dysphagia (transfer dysphagia) is not commonly reported in these patients[1]. Skeletal muscle dysfunction is manifest by preoesophageal dysphagia and tracheal aspiration which are due to pharyngeal dysfunction[12]. In oesophageal atresia the pharynx is unaffected by surgery and whether the loss of proximal oesophageal function alone causes symptoms remains uncertain.

Studies that evaluated function in repaired atresia confirm the almost universal incidence of motor abnormality affecting swallowing[1,2,7,13,14]. The immediate perianastomotic portions and the most proximal part of the distal oesophagus, the segments most mobilized during surgery, are the most severely affected[2]. Early reports emphasized the presence of distal oesophageal dysmotility. However, more recent studies indicate that this is more universal and that the proximal original pouch segment rarely contracts normally.

The oesophageal segments have to be mobilized during the repair. Extensive pouch mobilization is associated with severe motor disability. This is seen in patients who have had an oesophagostomy[13]. Although it has been established that deprivation dysphagia can partly be prevented by sham feeding, which aims to teach the person to initiate a primary peristaltic wave, motor nerve disruption must be a major component of this problem. Complete mobilization of the proximal pouch should be avoided, although the anastomosis must not be compromised. Mobilizing the distal oesophagus to obtain additional length could also have its consequences. Dysphagia of the transport type with or without gastro-oesophageal reflux could result[15]. Feeding difficulties are a major problem after repair in oesophageal atresia[14], although these symptoms tend to disappear with time[7].

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British Journal of Surgery 1996, 83, 1271–1275

Small intestinal myoelectrical activity and bacterial flora after Roux-en-Y reconstruction

E. SCHIPPERS, S. WILLIS, G. RUCKDESCHEL* and V. SCHUMPELICK

*Department of Surgery, Universitatsklinikum Rheinish Westphalian Technical University Aachen and *Max von Pettenkofer Institute for Hygiene and Medical Microbiology, Klinikum Großhadern, Ludwig Maximillian Universität Munich, Germany*

Correspondence to: Dr E Schippers, Department of Surgery, Universitatsklinikum Rheinish Westphelian Technical University Aachen, Pauwelsstrasse 30, 52057 Aachen, Germany

Small bowel myoelectrical activity and intestinal microflora were examined after partial gastrectomy and Roux-en-Y reconstruction in six dogs. Bacteriological analysis revealed a predominance of faecal bacteria. The basal electrical rhythm of the Roux limb was significantly decreased, while the frequency of phase III was increased ($P<0·05$). In the bypassed duodenum, activity fronts occurred in only 25 per cent of experiments. Food intake led to an increase in the mean(s.e.m.) motility index in the Roux limb (from 46·1(9·4) to 75·0(21·5), $P<0·05$), but not in the bypassed intestine (from 27·0(3·6) to 27·8(4·1), P not significant). Stimulation of the hypomotile bypassed intestine with cisapride induced an increase in the motility index from 27·0(3·6) to 111·2(16·5) ($P<0·001$).

The Roux-Y reconstruction is a common procedure in gastric and biliary surgery. The purpose of this reconstruction is to protect the oesophagus, gastric remnant or bile duct from nutrient or bile reflux by the propulsive peristalsis of the Roux limb. Nevertheless, after this technique some patients develop a symptom complex consisting of nausea, vomiting and, particularly, postprandial abdominal pain, the so-called 'Roux-Y syndrome'[1,2]. It has been hypothesized that these clinical symptoms are related to long-term changes in intestinal motility patterns accompanied by bacterial overgrowth in the upper gastrointestinal tract. Disturbed intestinal motility patterns in the fasting and postprandial state have been demonstrated in these patients[1]. Furthermore, Roux-en-Y reconstruction is often complicated by bacterial overgrowth[3,4].

The aim of the present experimental study was to examine the long-term changes in small intestinal myoelectrical activity after two-thirds gastric resection and Roux-en-Y reconstruction, and to determine consecutive changes in the bacterial flora in the upper gastrointestinal tract. A further aim was to examine the effect of a prokinetic agent on potentially disturbed motility patterns.

Materials and methods

Surgical procedure

After review and approval by the Animal Welfare Committee of the German government these experiments were performed under combined inhalation and intravenous anaesthesia (fentanyl–halothane) in male dogs weighing 10–15 kg In six dogs a median laparotomy was performed followed by two-thirds resection of the stomach. The duodenum was closed and intestinal continuity restored by a gastrojejunostomy with a jejunal loop, called the Roux limb. The duodenum and proximal jejunum were reanastomosed with the Roux limb 30 cm distal to the gastrojejunostomy by an end-to-side enteroenterostomy, forming a blind loop (*Fig. 1*). To monitor myoelectrical activity, six bipolar silver–silver chloride electrodes were implanted at equal distances (15 cm) on the serosal layer of the gastric remnant and the Roux limb, and two further electrodes were placed on the serosa of the bypassed intestine (*Fig. 1*). The cables led out of the abdomen on the left side and were brought subcutaneously to the interscapular region. They were connected to a recording plug fixed to a jacket. Four dogs with an intact

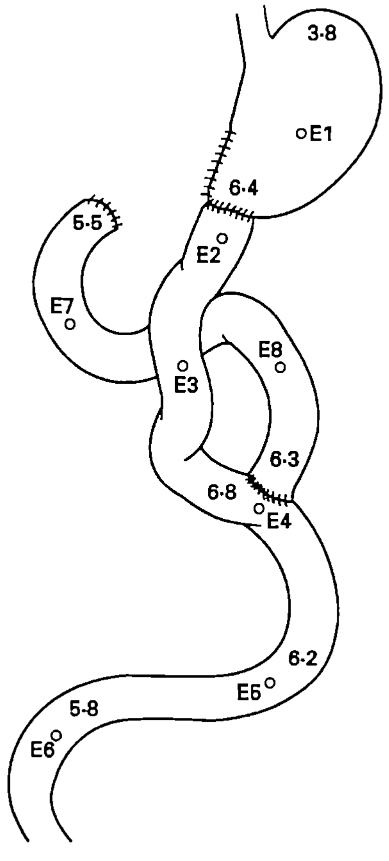

Fig. 1 Localization of the electrodes on the gastric remnant (E1), Roux limb (E2, E3), jejunum (E4–E6) and duodenum (E7, E8) after partial gastrectomy and Roux-en-Y reconstruction. Values in the various intestinal segments indicate the quantitative evaluation of bacterial overgrowth (mean colony-forming units)

Presented in part to the World Congress of Gastroenterology, Sydney, August 1990
Paper accepted 5 December 1995

gastrointestinal tract served as controls. They underwent implantation of eight electrodes at corresponding positions to the animals with a Roux limb.

Electromyography

Because of a strong correlation between myoelectrical and mechanical activity in the small intestine[5], electromyography was used to monitor motility patterns. Electrical signals were amplified and recorded online on an eight-channel polygraph (Hellige, Freiburg, Germany) with a paper speed of 5 mm/s. To identify the electrical spiking activity and the basal electrical rhythm (BER) a time constant of 0·03 s and an upper frequency limit of 30 Hz was chosen.

Visual analysis was carried out by two independent investigators. When analysis of a particular tracing differed between the two investigators, tracings were reviewed by both investigators together and a final common judgement was stated. For analysis, the appearance and periodicity of the migrating myoelectrical complex (MMC)[6], the duration of activity fronts (phase III), the propagation velocity of phase III and the calculated length of the activity front (duration × progression velocity) were determined. The various phases of the MMC in the interdigestive period were identified using the criteria of Code and Marlett[7] In addition the BER and its changes in each intestinal segment were determined. The postprandial 'fed pattern' was defined as random spiking activity and absence of the MMC[8]. For quantitative evaluation of different intestinal segments a myoelectrical motility index, defined as the number of spike potentials × spike width per 300 s, was calculated.

Experimental design

After a 2-week recovery period the myoelectrical activity of each animal was recorded five times in the fasting and postprandial period. For postprandial experiments a standardized (126 kJ (30 kcal) per kg body-weight) commercial meal (Waltham, Verden, Germany) with equal portions of fat, protein and glucose was used. The quantity of the test meal was calculated by the caloric value of the food (expressed as kcal per g food) and the body-weight of the dog. The meal was injected via an oro-oesophageal tube after identification of the first phase III of the MMC. Subsequently intestinal myoelectrical activity was recorded for 4 h The pharmacological effects of cisapride, a prokinetic agent, were also examined five times in every dog by injecting a bolus of cisapride 0 3 mg/kg intravenously after identification of the first phase III of the MMC Myoelectrical activity was recorded for two further periods of the MMC The experiments lasted for 6 months in each dog.

Bacteriological studies

For determination of the original bacterial flora in the upper gastrointestinal tract, a 1 × 1 cm^2 biopsy specimen from the stomach, duodenum and proximal jejunum was taken during operation in each dog Six months later, after termination of electromyographic recordings, a further laparotomy was performed and two biopsy samples from different locations of the same segments were taken. These were transported under anaerobic conditions (Port-A-Cul; Becton Dickinson, Heidelberg, Germany) to the microbiological laboratory and were cultured within 2 h. The biopsies were vigorously washed with stool buffer and the fluid obtained was inoculated with a spiral plater on various agar media selective for the main aerobic and anaerobic constituents of intestinal flora. The plates for aerobic organisms were incubated for 2 days, and those for anaerobes for up to 7 days until colonies were counted and identified. For quantitative evaluation, results were interpolated for up to 1 g of intestine and 1 ml of stool buffer. Results were given as $\log_{10}$ colony forming units (c.f.u.) of the various micro-organisms per gram of intestinal tissue. If the quantity in a single experiment was too small for evaluation, the detection threshold of the method, which was 1·0, was used.

Statistical analysis

Statistical analysis was performed with Friedmann's analysis or the Wilcoxon–Mann–Whitney *U* test as appropriate. $P<0\cdot05$ was considered significant. Results are given as mean(s.e.m.).

Results

All dogs survived the operation and remained healthy throughout the study period.

Basal electrical rhythm

The BER could be demonstrated constantly in every dog at every electrode. Its mean(s.e.m.) frequency was 18·5(0·5) per min in the duodenum, 14·0(0·2) per min in the Roux limb and 13·9(0·2) per min in the more distal jejunum. In comparison with controls there were no differences in the BER of the duodenum, whereas that of the proximal jejunum, the Roux limb, was significantly decreased (*Table 1*).

Fasting myoelectrical activity

The fasting myoelectrical activity of the small intestine was characterized by the periodic occurrence of the MMC in all dogs. After Roux-en-Y reconstruction a total of 135 MMCs with clear identification of phase III activity were registered. The activity fronts started below the gastroenterostomy and propagated aborally. Some 92 per cent of activity fronts registered at electrode E2 reached the distal electrode E6, and only 8 per cent terminated earlier.

Following the Roux operation there was a significantly increased frequency of phase III of the MMC. The mean(s.e.m.) interval between two periods of phase III activity was 64·4(3·1) *versus* 110·9(15·0) min in the control group (*Table 2*). Interindividual and intraindividual variations in duration, in propagation velocity and in the calculated wavelength of phase III were small. Differences from controls were not statistically significant (*Table 2*). In

Table 1 Frequency of slow waves in duodenum (E7), Roux limb (E2) and jejunum distal from the enteroanastomosis (E5)

	Frequency of slow waves per min		
Animal no.	Duodenum (E7)	Roux limb (E2)	Distal jejunum (E5)
Controls			
1	18·3(0·3)	17·6(0·1)	16·4(0·2)
2	18·6(0·3)	18·1(0·3)	16·9(0·2)
3	18·2(0·3)	17·5(0·2)	16·9(0·2)
4	18·5(0·3)	18·0(0·2)	16·0(0·2)
Overall	18·4(0·3)	17·8(0·2)	16·5(0·2)
Roux dogs			
5	18·8(0·5)	13·7(0·1)	13·6(0·2)
6	17·7(0·3)	14·1(0·2)	14·0(0·2)
7	19·0(0·4)	14·2(0·1)	14·1(0·1)
8	18·0(0·4)	13·7(0·3)	13·6(0·2)
9	18·7(0·6)	14·4(0·2)	14·0(0·3)
10	18·7(0·6)	14·0(0·3)	14·1(0·2)
Overall	18·5(0·5)	14·0(0·2)*	13·9(0·2)*

Values are mean(s.e.m.) of five measurements in each dog. *$P<0\cdot05$ (Roux dogs *versus* controls, Wilcoxon–Mann–Whitney *U* test)

Table 2 Characteristics of the migrating myoelectrical complex and phase III in the distal jejunum in controls and in the Roux limb after Roux-en-Y reconstruction

	MMC		Phase III	
Animal no.	Interval (min)	Duration (min)	Propagation velocity (cm/min)	Calculated wavelength* (cm)
Controls				
1	88·7(8·3)	5·3(0·2)	3·8(0·2)	20·2(0·7)
2	123·3(17·8)	5·0(0·1)	3·6(0·2)	17·7(0·6)
3	113·8(17·9)	5·5(0·1)	3·7(0·1)	21·2(0·5)
4	117·9(15·9)	5·4(0·1)	3·7(0·1)	19·7(0·5)
Overall	110·9(15·0)	5·3(0·1)	3·7(0·1)	19·7(0·6)
Roux dogs				
5	67·0(3·6)	5·8(0·4)	3·8(0·1)	21·7(1·1)
6	58·7(3·9)	5·2(0·3)	2·9(0·2)	15·2(1·3)
7	75·8(6·1)	3·7(0·2)	2·9(0·1)	9·3(0·9)
8	63·6(3·3)	5·2(0·1)	3·0(0·3)	15·4(0·9)
9	62·1(1·6)	5·2(0·2)	3·7(0·1)	19·0(0·7)
10	59·3(1·8)	4·0(0·1)	4·0(0·1)	16·0(0·6)
Overall	64·4(3·1)†	4·8(0·2)	3·4(0·1)	16·1(0·9)

Values are mean(s.e.m.) of five measurements in each dog. *Duration × velocity MMC, migrating myoelectrical complex †$P < 0·05$ (Roux dogs *versus* controls, Wilcoxon–Mann–Whitney *U* test)

contrast to the Roux limb and the distal jejunum, where the four phases of the MMC could be identified easily, almost no periodic MMCs occurred in the bypassed duodenum. During 135 registrations of phase III activity propagating from E2 to E6, distinct activity propagating from E7 to E8 was observed in only 23 recordings. A non-propagating phase III-like activity at E8 was observed in 11 recordings ($P < 0·01$). These activity fronts observed in the duodenum terminated at the enteroenterostomy.

Quantitative evaluation of myoelectrical motility patterns showed a corresponding picture. The calculated mean(s.e.m.) motility index was 46·1(9·4) in the Roux limb and 33·9(4·9) in the distal jejunum ($P < 0·05$). The motility index of the duodenum was significantly lower at 27·0(3·6) ($P < 0·001$) (*Fig. 2*).

Postprandial myoelectrical activity

Immediately after instillation of a standard meal, a 'fed pattern' could be observed in controls and in Roux dogs in the Roux limb and in the distal jejunum. The MMC was completely interrupted and substituted by a strong irregular spike activity in all segments. In 32 of 35 experiments this 'fed pattern' was persistent until the end of the experiment, when there was reappearance of the MMC in three cases. In the bypassed duodenum there was also a visible change in motility pattern. Because clear identification of the single phases of the MMC was not possible, even before food intake, this change was not so evident. Quantitative evaluation showed a significant 63 per cent postprandial increase in the mean(s.e.m.) motility index of the Roux limb from 46·1(9·4) to 75·0(21·5) ($P < 0·05$). In the jejunum there was a 36 per cent increase from 33·9(4·9) to 46·1(7·0) ($P < 0·05$), whereas there was no change in the duodenum (fasting 27·0(3·6) *versus* postprandial 27·8(4·1), P not significant) (*Fig. 2*).

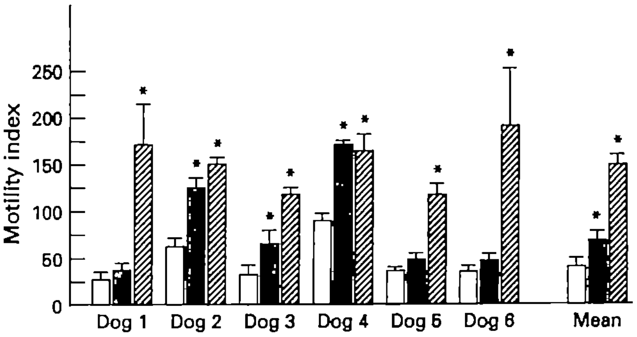

Fig. 2 Calculated motility index (spike potentials × spike width per 300 s) of the duodenum at E7 Roux-en-Y reconstruction in the interdigestive (□) and postprandial (■) periods and after administration of cisapride 0·3 mg/kg (▨). Values are mean(s.e.m.). *$P < 0·05$ *versus* fasting value (Wilcoxon–Mann–Whitney *U* test)

Table 3 Evaluation of bacterial overgrowth 6 months after Roux-en-Y reconstruction and relative contribution of aerobic and anaerobic species

	Anaerobes (%)	Aerobes (%)	Mean(s.e.m.) bacterial flora (c.f.u.)
Stomach			
Proximal	49	51	3·82(2·24)
Distal	49	51	6·35(1·05)*
Roux limb			
Proximal	51	49	7·08(1·25)
Distal	47	53	6·79(1·22)
Distal jejunum			
Proximal	54	46	6·23(1·05)
Distal	49	51	5·84(1·15)
Duodenum			
Proximal	58	42	5·53(2·05)
Distal	50	50	6·31(1·17)

c.f.u., Colony-forming units. *$P < 0·005$ (distal *versus* proximal stomach biopsy, Wilcoxon–Mann–Whitney *U* test)

Effect of cisapride

Intravenous injection of cisapride in a dose of 0·3 mg/kg induced strong spike activity in all intestinal segments. This effect could be demonstrated immediately after injection in all segments at the same time. This increase in spike activity was not as regular as the aboral propagation of spike activity in phase III of the MMC. Quantitative evaluation showed an increase in the motility index from twofold to 12-fold that of the controls. The mean(s.e.m.) motility index after application of cisapride was three to four times higher in all animals (*Fig. 2*): 144·2(11·1) in the Roux limb, 92·4(13·9) in the jejunum and 111·2(16·5) in the duodenum ($P < 0·001$).

Bacterial flora

Biopsies from the gastrointestinal wall taken during the two-thirds resection of the stomach and Roux-en-Y reconstruction served as controls. Bacteria were not detected in all specimens and, if present, only in very low numbers. Therefore control values were set to the detection threshold of the method at 1·0 c.f.u. In contrast,

Table 4 Differentiation of bacterial species in the upper gastrointestinal tract 6 months after Roux-en-Y reconstruction

	Colony-forming units			
Bacterial species	Stomach	Roux limb	Distal jejunum	Duodenum
Bacteroides	4·18 (3·00–6·51)	5·71 (3·90–7·70)	4·85 (3·70–6·40)	5·02 (3·00–6·51)
Anaerobic Gram-positive bacilli	3·14 (1·00–5·28)	3·41 (1·00–6·30)	3·20 (1·00–5·70)	3·68 (1·00–6·66)
Clostridia	2·88 (1·00–5·23)	4·36 (1·00–7·10)	3·27 (1·00–4·50)	3·10 (1·00–5·23)
Escherichia coli	4·35 (1·00–6·42)	5·85 (5·00–6·50)	4·25 (1·00–6·40)	3·53 (1·00–6·36)
Enterococci	3·85 (1·00–6·32)	3·60 (1·00–6·62)	3·34 (1·00–5·90)	3·63 (1·00–6·00)
Aerobic lactobacilli	3·17 (1·00–5·79)	3·44 (1·00–6·00)	3·20 (1·00–5·90)	3·05 (1·00–5·79)

Values are mean (range) of two biopsies from each intestinal segment

high numbers of organisms were detected in the stomach, Roux limb, jejunum and duodenum 6 months after operation. Quantification of bacterial colonization showed differences depending on the intestinal segments from which the biopsies had been taken. The highest numbers of micro-organisms were found near the gastrojejunostomy with 7·1 c.f.u., and the lowest were in the gastric fundus with 3·8 c.f.u. ($P<0\cdot05$). There were no significant differences in bacterial counts between Roux limb, duodenum and jejunum (*Fig. 1*). The increase in the bacterial flora was similar in aerobic and anaerobic bacteria (*Table 3*), with *Bacteroides* species, *Clostridia* and non-sporing Gram-positive rods such as bifidobacteria and eubacteria growing as anaerobes and *Escherichia coli*, enterococci and lactobacilli as aerobes (*Table 4*).

Discussion

Disturbed intestinal motility occurs in patients who have undergone Roux-en-Y reconstruction. Mathias *et al.*[1] described a 'Roux-Y syndrome', which is characterized by chronic abdominal pain, constant nausea and intermittent postprandial vomiting. Gustavsson and co-workers[9] evaluated patients with Roux-en-Y reconstruction retrospectively for these symptoms. Although they reported excellent functional results in about two-thirds of all patients, 30 per cent of those with gastrojejunostomy and 8 per cent with oesophagojejunostomy suffered from the Roux-Y syndrome. Scintigraphic studies in humans after Roux-en-Y reconstruction have shown normal[2] as well as delayed[10–12] or accelerated[11] emptying. The results of manometric studies in symptomatic patients after the Roux operation, demonstrating disturbed interdigestive motility without regular MMCs and the absence of a 'fed pattern' in symptomatic patients, are, however, more definite[1,12–14].

In electromyographic recordings after Roux-en-Y reconstruction in the present study, the activity front was propagated from the Roux limb to the distal jejunum without impairment. The increased frequency of the MMC in these dogs was in accordance with observations in patients after Roux-Y gastrectomy[15]. Food intake interrupted the MMC and led to the appearance of the typical 'fed pattern'. These data accord with reports of electromyographically normal intestinal motility in the Roux limb in asymptomatic patients[16].

Descriptions of retrograde propagation of jejunal electrical slow waves and spike bursts in dogs[17,18] and in symptomatic patients[19] suggest that these abnormalities might contribute to the Roux-Y stasis syndrome. A return of the BER was not observed in this study, possibly because the electrodes were too far apart. However, retrograde propagation of basal electrical activity has also been reported in intact dogs[17]. Nevertheless there was a significant decrease in the frequency of the BER in the proximal Roux limb, indicating that interruption of intestinal continuity might lead to loss of stimulation by the intestinal pacemaker in the duodenum[20].

In the present experiments there was a highly significant decrease in myoelectrical activity in the bypassed duodenum. Under fasting conditions, phase III activity could be identified clearly in only 25 per cent of experiments. After food intake there was also no adequate increase of electrical activity in the duodenum. This could be explained in part by exclusion of the duodenum. The direct contact of food with the duodenal mucosa as a decisive stimulus for postprandial motility is missing. Duodenal hypomotility could lead to delayed transport of bile and pancreatic enzymes, and consecutively to asynchronous gastric emptying and secretion of bile and pancreatic enzymes, inducing steatorrhoea, postprandial nausea and flatulence. In support of this hypothesis, Bradley *et al.*[21] demonstrated significantly decreased trypsin and lipase concentrations in the jejunum of patients with Roux-en-Y reconstruction.

Cisapride stimulated motility in all segments of the small intestine in the present experiments. In humans, stimulation of intestinal motility by cisapride occurs with accelerated intestinal transit[22]. Therefore, cisapride might be useful in the treatment of functional disorders in patients having Roux-en-Y reconstruction.

The long-term complications of gastric surgery, such as steatorrhoea, diarrhoea and impaired absorption of vitamin B_{12}, may be the result of abnormal proliferation of bacteria in the upper intestinal tract. In the present study overgrowth with a typical faecal flora of aerobic and anaerobic bacteria was observed. The dominant species were *Bacteroides* and *E. coli*, as reported previously[3,4,21]. Bacterial overgrowth may be facilitated by intestinal motility disorders. It has been hypothesized that the MMC can no longer fulfil its 'housekeeper' function[23]. Scintigraphic studies in patients with Roux-en-Y biliary–enteric anastomosis, demonstrating a hypomotile loop[24] and a high rate of cholangitis[25], are in accord with this theory. In the present study, however, demonstration of the same extent of typical faecal flora in the hypomotile duodenum and in the Roux limb cannot be explained by this theory alone.

Gastric stasis and reduction of acid production are also possible mechanisms for bacterial overgrowth in the upper gastrointestinal tract. In contrast to humans, the gastric mucosa of the dog possesses parietal cells in the fundus of the stomach, so that a two-thirds resection would not lead to achlorhydria. Furthermore, there are descriptions of achlorhydria in humans without bacterial overgrowth[3]. However, the remaining acid production of the gastric fundus could have been responsible for the relative decrease of bacterial overgrowth in this study.

Acknowledgements

This work was supported in part by a grant from the Deutsche Forschungsgemeinschaft (Schi 231/2-1).

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British Journal of Surgery 1996, 83, 1276–1278

Upper oesophageal sphincter function during general anaesthesia

J. P. McGRATH, C. McCAUL*, P. J. BYRNE, T. N. WALSH and T. P. J. HENNESSY

*University Departments of Surgery and *Anaesthesia, St James's Hospital, Dublin 8, Ireland*
Correspondence to: Mr T. N. Walsh

The effect of anaesthesia on the upper oesophageal sphincter response to acid in the distal oesophagus and hypopharynx, and the effect of atracurium besylate on acid migration into the hypopharynx, was studied in 102 patients undergoing elective varicose vein surgery. Group 1 ($n = 48$) received a general anaesthetic and the muscle relaxant atracurium besylate whereas group 2 ($n = 54$) received a general anaesthetic without relaxation. Upper oesophageal sphincter tone was significantly lower in patients receiving muscle relaxants ('sphinctometer output', eight *versus* 14, $P<0{\cdot}05$). Sixteen patients (16 per cent) had reflux into the distal oesophagus during anaesthesia (nine in group 1 and seven in group 2, P not significant), of whom seven had reflux to the hypopharynx. There was no difference in incidence of hypopharyngeal acid exposure between groups. Upper oesophageal sphincter tone did not alter in response to reflux into the distal oesophagus or hypopharynx in either group. The upper oesophageal sphincter fails to protect the hypopharynx under general anaesthesia even if patients do not receive a muscle relaxant.

The upper oesophageal sphincter (UOS) is a high-pressure zone between the pharynx and oesophagus which helps protect the respiratory tract from aspiration of gastric refluxate and prevents entry of air into the oesophagus during inspiration[1,2]. Aspiration is a greater risk if gastric refluxate transgresses the UOS. During anaesthesia the risk of aspiration increases; this is thought to result from the effect of anaesthetic agents and muscle relaxants on the UOS, as most have been shown to reduce UOS pressure[3–6]. UOS pressure has been shown to increase in response to both gastro-oesophageal reflux and oesophageal acid infusion[7,8]. The effect of general anaesthesia and muscle relaxants on this response is unknown.

The UOS has proved difficult to study. There is considerable axial and radial asymmetry, explaining the variability of results using station perfusion manometry as pressure readings depend on the direction of the catheter, with higher pressures directed anteroposteriorly. The speed and range of movement of the sphincter make it almost impossible to maintain the position of the transducer or perfused catheter in the high-pressure zone for prolonged periods. The only system that hitherto allowed prolonged studies was the Dent sleeve but this is unphysiological and requires the patient to remain supine throughout the study[9,10]. With the development of solid-state circumferential transducer technology more accurate studies of UOS function are now possible[2].

The sphinctometer is a 6-cm oil-filled device that allows determination of sphincter tone[11]. It has been used previously for the study of lower oesophageal sphincter (LOS) function[12–15]. In this study it was employed to evaluate UOS function in response to muscle paralysis and oesophageal acid reflux. The effect of muscle paralysis on the pattern of gastro-oesophageal reflux into the distal oesophagus and hypopharynx under anaesthesia was also examined.

Patients and methods

All patients admitted for elective varicose vein surgery over a 6-month period were invited to participate in the study. All were American Society of Anesthesiologists grade I or II. Patients receiving any medication 24 h before surgery, those with a history of previous upper gastrointestinal surgery and those requiring laryngeal mask or epidural anaesthesia were all excluded from the study. The study was approved by the hospital ethics committee and informed consent was obtained from all participants.

Study groups

Patients were subdivided into two groups based on whether or not a muscle paralysing agent was used during anaesthesia. Group 1 ($n = 48$) received a paralysing agent in addition to general anaesthetic and group 2 ($n = 54$) received a general anaesthetic only. The decision to paralyse was based on the need for patients to have short saphenous vein surgery in addition to long saphenous vein ligation, and to be positioned prone for the second stage of the operation.

Median age was 32 years: 29 (range 19–67) years in group 1 and 34 (range 27–59) years in group 2 (P not significant). There were 33 women in group 1 and 30 in group 2 (P not significant).

Of 102 patients selected for the study 27 admitted to symptoms suggestive of gastro-oesophageal reflux. This included heartburn in 16, regurgitation in four, and heartburn and regurgitation in seven. Eight of these 27 patients took occasional medication, which included antacids in five and H_2-receptor antagonists in three. All described symptoms as mild and intermittent except one patient who had completed two courses of antacids. No patient recruited for the study was receiving medication at the time of admission to hospital. The 27 patients were randomized to groups 1 and 2 based on the need for short saphenous vein surgery. In this manner 15 were randomized to group 1 and 12 to group 2 (P not significant). For the purpose of this study, only recordings made during the initial supine period were analysed. All patients were studied in the supine position with the head on a single pillow.

Anaesthesia

Premedication consisted of diazepam 10 mg orally 40 min before surgery. Propofol 2·0–2·5 mg/kg, fentanyl 1 mg/kg and suxamethonium 1 mg/kg were given intravenously at induction. Anaesthesia was maintained with nitrous oxide and isoflurane. Atracurium 0·05 mg/kg was given to patients requiring a paralysing agent and morphine 2·5 mg was administered intravenously immediately before the incision was made.

pH measurement and manometry

A lubricated split rubber tube was passed orally into the

Paper accepted 11 December 1995

oesophagus. The sphinctometer and two antimony probes were passed through the rubber tube into the stomach. A pH less than 2 confirmed placement of the probes in the stomach. After allowing approximately 5 min for stabilization of the sphinctometer at body temperature, it was slowly withdrawn and the high-pressure zone (HPZ) of the LOS was identified and pressures recorded. Withdrawal of the sphinctometer into the oesophagus was followed by localization of the HPZ at the UOS. The area of highest recording within this HPZ was taken at the UOS Following identification of the sphincters the antimony probes were placed 5 cm above the LOS and 2 cm above the UOS, and the study commenced.

The sphinctometer gives a reading that is directly proportional to sphincter tone and is measured as 'sphinctometer output' (SO)[11]. Readings were taken until reversal of anaesthesia or until patients requiring short saphenous surgery were placed in the prone position.

Data analysis

Data were stored during the study on a motility digitrapper (Synectics, Stockholm, Sweden) and dual-channel pH digitrapper mark II (Synectics), downloaded on to a personal computer and analysed with Gastrosoft Software (Synectics). Results were expressed as median and range. The Mann–Whitney *U* test was used to compare groups.

Results

Data from 102 patients (63 women) with a median age of 32 (range 19–67) years was evaluable. Median study duration was 44 (range 22–117) min (*Table 1*). Thirty-two patients were lost from the study because of violation of the anaesthesia protocol (19), failure of intubation (seven), gastric pH greater than 2 (three) and sphinctometer drift (three).

Sixteen patients had reflux into the distal oesophagus. In nine of these reflux was documented in the distal oesophagus only; these patients were termed 'distal refluxers'. In seven the refluxate migrated proximally to the hypopharyngeal region and these patients were termed 'hypopharyngeal refluxers'. All pharyngeal reflux episodes were preceded or accompanied by a drop in pH to less than 4 in the distal oesophagus. There was no significant difference in the incidence of either distal (19 *versus* 13 per cent) or hypopharyngeal (6 *versus* 8 per cent) reflux between patients receiving and those not receiving muscle relaxants. The presence of symptoms suggestive of gastro-oesophageal reflux was not predictive of reflux episodes under general anaesthesia. The incidence of oesophageal reflux was similar in those with and without symptoms: four of 27 compared with 12 of 75 patients. The incidence of hypopharyngeal reflux was also similar: two of 27 symptomatic compared with five of 75 asymptomatic patients (*P* not significant).

Table 1 Reflux episodes and sphincter tone

	Paralysed ($n = 48$)	Non-paralysed ($n = 54$)
No. of patients with distal reflux*	9 (19)	7 (13)
No. of patients with hypopharyngeal reflux*	3 (6)	4 (7)
Upper oesophageal sphincter tone (SO)†	8 (4–11)	14 (10–19)‡
Lower oesophageal sphincter tone (SO)†	10 (8–14)	9 (6–15)
Duration of study (min)†	42 (24–95)	49 (22–117)

*Values in parentheses are percentages; †values are median (range). SO, 'sphinctometer output'. ‡$P < 0{\cdot}05$ *versus* paralysed (Mann–Whitney *U* test)

Median UOS tone was 14 (range 0–22) SO. It was significantly lower in patients receiving a paralysing agent (8 (range 4–11) SO) than in those not receiving a muscle relaxant (14 (range 10–19) SO) ($P < 0{\cdot}05$). UOS tone was not affected by reflux into the distal oesophagus or the hypopharynx. No change or alteration in UOS recordings was noted before, during or after reflux episodes. Median LOS tone was 9 (range 6–15) SO. Patients with hypopharyngeal reflux showed no difference in UOS tone, LOS tone or distal oesophageal acid exposure compared with those with distal oesophageal reflux alone.

Discussion

The patterns of gastro-oesophageal reflux under general anaesthesia reported in the literature are difficult to interpret because of variability in incidence, ranging from 0·5 to 42 per cent. This may reflect differing study populations, surgical and anaesthetic practices, or recording and interpretive techniques[16–18]. The incidence of 16 per cent (16 of 102) in this study is lower than that reported by others but as this study population was homogeneous and without significant morbidity it may reflect a true incidence. Seven of the 16 patients with distal gastro-oesophageal reflux also had migration of acid into the hypopharynx. The overall incidence of hypopharyngeal reflux was therefore 7 per cent. Proximal migration of refluxate may reflect compromised clearance mechanisms such as pharyngeal swallowing and secondary oesophageal peristalsis which are known to be impaired by anaesthesia[19,20].

The relationship between gastro-oesophageal reflux and UOS function in the waking state is unclear. Hunt *et al.*[7] reported that UOS pressures were significantly higher in patients with gastro-oesophageal reflux than in normal subjects. Others[21,22] have shown that intraoesophageal acidification may lead to increased UOS pressure. A number of studies, however, have failed to demonstrate such a rise in pressure[8,23]. In addition, studies that examined reflux episodes as opposed to oesophageal acidification have failed to demonstrate an UOS response to reflux[21,22,24]. These differences may reflect the limitations of previously available recording techniques which have relied exclusively on perfusion manometry. In this study the UOS showed no response to either distal oesophageal or hypopharyngeal reflux episodes during general anaesthesia. This has not been demonstrated previously.

Muscle relaxants had no effect on LOS pressure. This is consistent with previous studies showing that the LOS is not affected by atracurium besylate, or other non-depolarizing muscle relaxants, as it is composed of smooth muscle[27]. Consequently there was no detectable difference in distal oesophageal acid exposure in those receiving muscle relaxation. In contrast, the pressure of the UOS is significantly lower in patients receiving muscle relaxants[28]. This is consistent with the known actions of atracurium besylate on striated muscle.

Muscle relaxants did not increase the incidence of hypopharyngeal reflux. It is not clear why refluxate crossed the UOS into the hypopharynx in some patients. Distal oesophageal acid exposure was similar in both distal and hypopharyngeal refluxers. In addition, sphincter pressures did not differ significantly.

Oesophageal reflux migrates to the hypopharyngeal region in a significant proportion of patients. The oesophageal body and sphincters fail to protect the hypopharyngeal region. In spite of the absence of pharyngeal activity in these patients the duration of hypopharyngeal reflux episodes was very short. As clinical complications occur infrequently it is likely that other mechanisms such as salivary or bicarbonate secretion act as protective mechanisms. With migration of more than 40 per cent of reflux episodes into the hypopharynx, UOS function is compromised by anaesthesia and affords little protection from aspiration.

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British Journal of Surgery 1996, 83, 1279–1283

Free revascularized jejunal loop repair following total pharyngolaryngectomy for carcinoma of the hypopharynx: report of 90 patients

A. S. JONES, N. J. ROLAND, D. HUSBAND*, J. W. HAMILTON and I. GATI

*Department of Otolaryngology, University of Liverpool and *Clatterbridge Centre for Clinical Oncology, Clatterbridge Hospital, Bebington, Wirral, UK*

Correspondence to: Professor A. S. Jones, Department of Otolaryngology, University of Liverpool, The Royal Liverpool University Hospital, PO Box 147, Liverpool L69 3BX, UK

Ninety patients with carcinoma of the hypopharynx underwent pharyngolaryngectomy and reconstruction with a jejunal free autograft. Fifty-five patients had primary surgery and 35 salvage surgery for recurrence after radiotherapy. Following primary surgery 28 patients had postoperative radiotherapy and 27 did not. Complications occurred in 51 per cent of patients, the most common being necrosis of the jejunal graft (19 per cent); 12 per cent developed significant stenosis and 4 per cent died in the perioperative period. Eleven per cent of patients developed a fistula. The total number of complications diminished as the experience of the unit increased. Median follow-up was 4·9 years. Of patients treated with primary surgery, 48 per cent developed primary site recurrence (at 3 years) and 53 per cent neck node recurrence (at 5 years). The tumour-specific 5-year survival rate for all patients was 42 per cent. Following primary surgery 28 per cent survived for 5 years and after salvage surgery the rate was 59 per cent. Positive resection margins and extensive neck disease adversely affected survival ($P = 0{\cdot}02$ and $P = 0{\cdot}001$ respectively). The free revascularized jejunal graft is a safe and predictable method of repair following total pharyngolaryngectomy.

Carcinoma of the hypopharynx is a rare disease with an incidence in the UK[1] of approximately 1 in 100 000. Individual experience with this condition is often limited and treatment may be substandard with correspondingly poor results.

Hypopharyngeal carcinoma generally has a poor prognosis even with aggressive treatment and most patients are dead within 1 year of diagnosis[2]. Because of the low survival rate, high recurrence rate and generally high treatment morbidity, the choice of therapy is particularly important. Early hypopharyngeal cancer may be treated by irradiation, with the option of salvage surgery if recurrence supervenes[3–7]. It has been stated that radiotherapy should be reserved for patients without enlarged lymph nodes[8] but it has also been suggested that radiotherapy can be given for a small primary tumour and radical neck dissection subsequently performed for nodal metastases[6,7,9]. Surgical resection is preferred for large tumours or in the presence of bulky cervical metastases[10,11].

Small posterior pharyngeal wall tumours can be resected via a lateral pharyngotomy with preservation of the larynx[12,13]. More extensive and circumferential lesions require total pharyngolaryngectomy. A variety of techniques of pharyngeal reconstruction have been described but interposition of stomach, small bowel or colon[14–16] is considered the best option. This paper presents a large series of over 10 years' experience with the free jejunal graft for pharyngeal reconstruction after pharyngolaryngectomy for carcinoma which many consider the superior method of repair[17–23].

Patients and methods

Ninety patients were included in the study. Fifty-five received surgery as primary treatment, 28 had postoperative radiotherapy and 27 had none. No patient had planned combined treatment with preoperative radiotherapy. Thirty-five patients were treated with primary irradiation with curative intent and later developed a local recurrence which was managed by pharyngolaryngectomy and jejunal loop repair.

The stage of the tumour at presentation was determined using the Union Internacional Contra La Cancrum classification[24], and the general physical condition with the method recommended by the Eastern Cooperative Oncology Group[25]. Histological grade was assigned into well, moderately or poorly differentiated squamous cell carcinoma but in some cases no grade was given. All data were stored on a microcomputer database and the date of death and follow-up times recorded from clinic visits, general practitioner records, the Merseyside and Cheshire Cancer Registry, and Office of Population Censuses and Surveys data. No patient was lost to follow-up.

The technique of total pharyngolaryngectomy has been described elsewhere[26], as has the method of free revascularized jejunal loop repair[27]. Frozen-section histological examination of the resection margins has been carried out routinely only for the past 5 years. Before that it was performed only when clinically appropriate.

Briefly, the harvested segment of jejunum was usually based on the second jejunal artery and vein. The graft was interposed between the pharynx and upper oesophagus, the lower anastomosis was made with 3·0 polyglactin placed as a single layer of approximately 12 interrupted sutures, and the upper anastomosis was performed with a continuous single layer of 3·0 polyglactin suture, locked regularly. The anterior wall in proximity to the base of the tongue was reinforced with interrupted polyglactin sutures. The microvascular anastomosis was made in all cases using 9 0 monofilament polypropylene sutures using the 120° technique. Donor arteries were usually superior thyroid or lingual, and occasionally the facial. The donor vein was usually the external jugular, or a convenient branch of the internal jugular or superior thyroid veins. If none of these was available, the internal jugular vein itself was utilized by an end-to-side technique. All patients received intravenous antibiotics (usually cefuroxime and metronidazole) and all had dextran 40 (500 ml daily for 3 days).

When postoperative radiotherapy was employed, the dose ranged from 55 Gy given over 15 fractions to 60–66 Gy given as 25 to 35 fractions. The patient was immobilized in a beam-

Paper accepted 3 December 1995

directing plastic shell and treated using anterior oblique double-wedged fields.

Data were transferred from the database to the SAS statistical package on a Pentium microcomputer (Statistical Analysis System, version 6 03; SAS Institute, Cary, North Carolina, USA)[28]. Various host and tumour factors were included in the analysis (*Table 1*)

Categorical data were displayed in contingency tables and analysed by χ^2 test with Yates correction. Factors associated with complications were analysed by categorical modelling (the CATMOD procedure)[28] and the same method was used to analyse differences between patients receiving radiotherapy or no radiotherapy Survival curves were constructed using the life-table method[29] with the LIFETEST procedure[28] and differences in survival curves analysed with the log rank test[28,30]. While crude recurrence rates are given, actuarial development of recurrence is also quoted using the life-table method (LIFETEST)[28] The calculations are given only for the patients treated by primary surgery, as all those who had primary radiotherapy developed recurrence Factors associated with survival were further analysed by means of Cox's proportional hazards model[31].

Results

The study included 90 patients treated by total pharyngolaryngectomy and free revascularized jejunal loop repair. All but 13 procedures were done for carcinoma of the hypopharynx. Of the remainder, ten had carcinoma of the cervical oesophagus and three carcinoma in a pharyngeal remnant following total laryngectomy. All but two procedures were done for squamous cell carcinoma. Median hospital stay was 16 (range 11–90) days. Median potential follow-up was 4·9 years.

Host and tumour factors for the primary surgery ($n = 55$) and salvage surgery ($n = 35$) groups are detailed in *Table 1*. The salvage surgery group contained significantly more patients with carcinomas at sites other than the hypopharynx, for example cervical oesophagus or pharyngeal remnant ($\chi^2 = 15{\cdot}67$, 3 d.f., $P = 0{\cdot}001$). There was no difference in nodal status between patients having primary or salvage surgery at the time of primary treatment, i.e. surgery or radiotherapy. There was a significant difference between the tumour stage of the two groups at the time of surgery. There were fewer patients with neck node metastases at the time of primary site recurrence in patients having salvage surgery ($\chi^2 = 5{\cdot}89$, 1 d.f., $P = 0{\cdot}02$). In addition, patients in the salvage surgery group suffered fewer recurrences at the primary site than those in the primary surgery group ($\chi^2 = 4{\cdot}15$, 1 d.f., $P = 0{\cdot}04$).

Patients who had primary surgery followed by no adjuvant treatment were compared with those who had primary surgery followed by radiotherapy. Significant difference in clinical details existed only for sex: patients who had postoperative radiotherapy were mostly men ($\chi^2 = 5{\cdot}60$, 1 d.f., $P = 0{\cdot}02$).

Table 1 Host and tumour factors in patients having free revascularized jejunal loop repair following total pharyngolaringectomy

Factor	Primary surgery ($n = 55$)	Salvage surgery ($n = 35$) At presentation	At recurrence	
Sex				
Male	36	23		
Female	19	12		
Age (years)				
<60	29	16		
>60	26	19		
Performance status (ECOG)				
0	43	11		
1–4	12	1		
Referred from elsewhere	0	23		
Site				
Postcricoid	24	11		*
Piriform fossa	27	10		
Post wall	2	3		
Other	2	11		
UICC staging				
Primary tumour				*
T_{1-2}	15	8	14	
T_{3-4}	40	4	21	
Referred from elsewhere	0	23	0	
Neck node metastases				
N_0	27	8	27	
N_+	28	4	8	
Referred from elsewhere	0	23	0	
Histology				
Well differentiated	10	2		
Moderately differentiated	27	21		
Poorly differentiated	8	10		
No grade assigned	10	0		
Non-squamous malignancy	0	2		
Extracapsular rupture				
Yes	15		4	
No	13		4	
Resection margins involved				
Yes	7		3	
No	48		32	
Recurrence at primary site				
Yes	20		6	*
No	35		30	
Neck node recurrence				
Yes	12		5	
No	43		30	
Distant metastases				
Yes	10		6	
No	46		29	

ECOG, Eastern Cooperative Oncology Group; UICC, Union Internacional Contra la Cancrum; Post wall, posterior pharyngeal wall. *$P < 0{\cdot}05$ *versus* primary surgery (χ^2 test)

The actuarial development of recurrence at the primary site and in neck nodes for patients treated by primary surgery is shown in *Fig 1* The recurrence rate at the primary site was 48 per cent at 3 years and in the neck 53 per cent at 5 years. *Fig. 2* shows the effect of adjuvant postoperative radiotherapy. At 2 years patients who had postoperative irradiation had a 27 per cent recurrence rate at the primary site compared with 35 per cent in those who did not. The differences were not, however, significant ($\chi^2 = 0{\cdot}50$, 1 d.f, $P = 0{\cdot}48$). At 2 years 24 per cent of patients who had postoperative radiotherapy developed a neck node recurrence compared with 31 per cent of those who did not ($\chi^2 = 0{\cdot}10$, 1 d.f., $P = 0{\cdot}75$).

Multiple logistic regression using categorical modelling demonstrated no significant host or tumour factors associated with recurrence either at the primary site or in the neck in patients who had primary surgery.

The complications for all 90 procedures are shown in *Table 2*. There were no significant differences in the complication rates between patients having primary or salvage surgery. The complication rate reduced as experience increased: the first 45 patients treated in this unit had a complication rate of 56 per cent whereas the

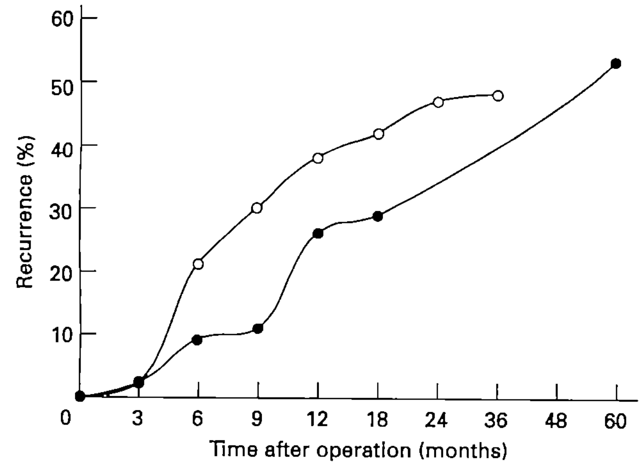

Fig. 1 Actuarial development of recurrence at primary site (○) and in neck nodes (●) in 55 patients treated by primary total pharyngolaryngectomy

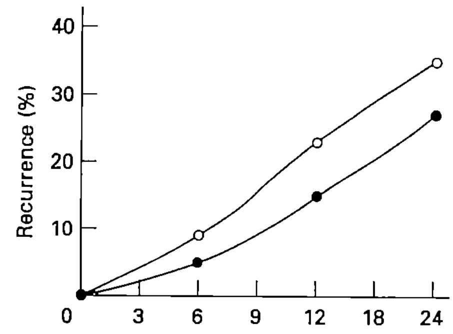

Fig. 2 Actuarial development of primary site recurrence in 55 patients treated by primary surgery. effect of postoperative radiotherapy (○), No radiotherapy ($n = 27$); (●), radiotherapy ($n = 28$). $\chi^2 = 0{\cdot}50$, 1 d.f., $P = 0{\cdot}48$

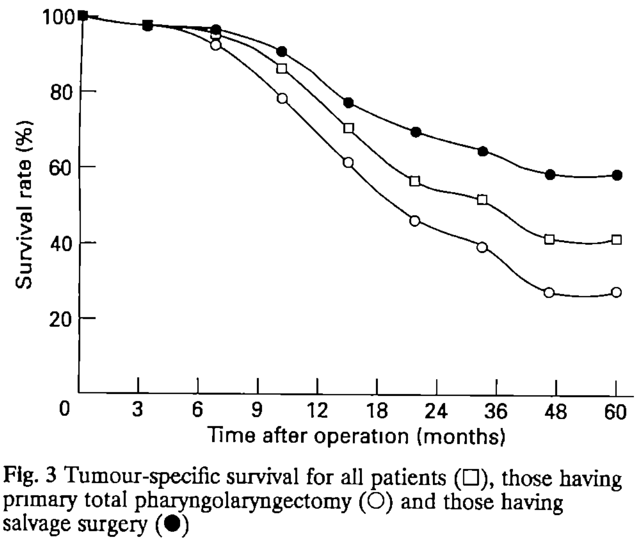

Fig. 3 Tumour-specific survival for all patients (□), those having primary total pharyngolaryngectomy (○) and those having salvage surgery (●)

most recent 45 had a rate of 47 per cent ($\chi^2 = 0{\cdot}40$, 1 d.f., $P = 0{\cdot}53$). Twelve per cent of patients developed stenosis severe enough to require dilatation. Sixty per cent were able to eat a reasonably normal diet, although not all could eat meat. No patient had complete dysphagia.

Table 2 Complications of total pharyngolaryngectomy with free revascularized jejunal loop repair

Complication	All patients* ($n = 90$)	Primary surgery ($n = 55$)	Salvage surgery ($n = 35$)	χ^2	d f	P
Necrosis	17 (19)	8	9	1·09	1	0·30
Stenosis	11 (12)	8	3	0·26	1	0·61
Fistula	10 (11)	5	5	0·18	1	0·67
Perioperative death	9 (10)	5	4	—	—	—
Medical problems	3 (3)	3	0	—	—	—
Carotid artery rupture	1 (1)	1	0	—	—	—
Total no of patients with complications	46 (51)	30	16	0·36	1	0·55

Values in parentheses are percentages. *Some patients in the salvage surgery group had more than one complication

Table 3 Cox regression: factors affecting survival of 90 patients

Variable	Estimate	P
Age	−0·17	0·56
Sex	0·23	0·13
Site: postcricoid *versus* piriform fossa	0·43	0·25
Histological grade	0·30	0·12
Tumour stage	−0·33	0·09
Positive resection margin	−0·19	0·02
Performance status	0·19	0·32
Stage of neck node metastases	0·10	0·33
Histological stage of neck dissection	−0·13	0·001
Primary surgery *versus* primary radiotherapy*	1·67	0·0004

*Primary radiotherapy gave a better cure rate than primary surgery but this was a biased group as only patients with recurrence at the primary site were included, not those dying after radiotherapy

When patients who had stenosis before radiotherapy were excluded from the group of 55 patients having primary surgery there was no significant direct effect of radiotherapy on the rate of stenosis ($\chi^2 = 0{\cdot}96$, 1 d.f., $P = 0{\cdot}33$).

The graft necrosis rate was 19 per cent but results improved dramatically with experience. The rate was 31 per cent for the first 45 patients but fell to 4 per cent for the second 45.

Host and tumour factors associated with flap necrosis, fistulas and stenosis were analysed by multiple logistic regression; there were no significant associations.

Of patients having primary surgery, 27 had no neck node metastases whereas 28 had enlarged neck nodes at the time of surgery; in the salvage surgery group the values were 27 and eight respectively. Nearly all patients with neck node metastases were treated by radical neck dissection and all patients had positive histological results. Thirty-one of the 34 patients in the primary surgery group having treatment to the neck had a radical neck dissection; one patient had bilateral radical neck dissection, one an extended radical neck dissection and one a modified neck dissection. Extracapsular rupture was demonstrated histologically in 16 cases. Of patients who had primary radiotherapy, two had a radical neck dissection and two radiotherapy to the neck. Eight patients having salvage surgery also had radical neck dissection, three of them bilateral.

The observed survival rate of all patients at 5 years was 17 per cent (95 per cent confidence interval (c.i.) 9–26 per cent). Following primary surgery the survival rate was 11 (95 per cent c.i. 4–21) per cent, and after salvage surgery 29 (95 per cent c.i. 14–44) per cent. For all patients the tumour-specific survival rate was 42 (95 per cent c.i. 23–58) per cent. After primary surgery this was 28 (95 per cent c.i. 10–48) per cent and after salvage surgery 59 (95 per cent c.i. 31–78) per cent (*Fig. 3*).

The 3-year tumour-specific survival rate in patients who had postoperative radiotherapy was 32 per cent and in those who did not have radiotherapy it was 38 per cent ($\chi^2 = 0\cdot14$, 1 d.f., $P = 0\cdot71$).

Survival data were further analysed using Cox's proportional hazards model and the various statistics are tabulated in *Table 3*.

Discussion

This department started using the technique of free jejunal grafting in 1967 but had little success initially because of lack of experience in microvascular techniques. The present paper does not address the relative merits of surgery *versus* radiotherapy, as these have been covered in other publications from this unit[5–7,13].

The present study demonstrates that primary surgery tends to be used for cricopharyngeal cancer and radiotherapy for tumours in other sites. In addition, patients with more advanced tumours tend to have primary surgery, and those with early tumours have primary radiotherapy. There is a tendency for patients with neck node metastases to have surgery. The overall cure rate for hypopharyngeal cancer is relatively poor; half the patients in this series were dead within 18 months. It is not the policy of this department to carry out total pharyngolaryngectomy and repair with free revascularized jejunal loop as a palliative procedure in a patient known to be dying from the disease. Stringent efforts are made to stage the disease adequately, including computed tomography of the lungs, ultrasonography of the liver and bone scanning when bulky disease is present. Of patients who are potentially curable, only just over 40 per cent are actually cured by total pharyngolaryngectomy with free revascularized jejunal loop.

The complication rate is high: only 49 per cent of patients have no complications. This value, however, compares favourably with that from other series[32,33]. The fistula rate in the present series was low compared with that in others[22,34–38], as was the perioperative mortality rate (4 per cent)[32,35,39]. Sixty per cent of patients were able to eat a normal diet, but 12 per cent had stenosis severe enough to require endoscopic dilatation, similar to other studies[22,35,37,38,40,41]. Speech was not specifically studied in the present paper but is known to be relatively poor following jejunal repair[42]. Some 30 per cent of patients in whom tracheal oesophageal valve rehabilitation is attempted develop intelligible speech[43].

The primary site recurrence rate in the present series was 48 per cent after 3 years following which no further recurrences occurred. In the neck, recurrence occurred for up to 5 years, to reach an overall rate of 53 per cent. Radiotherapy appeared to reduce this recurrence rate at the primary site from 35 to 27 per cent, and the rate of neck node recurrence from 31 to 24 per cent.

Cure rates in the present series were satisfactory with a tumour-specific survival rate of 57 per cent at 2 years and 42 per cent at 5 years, which compares favourably with other series[23,32,35,44]. Patients who were treated by primary surgery had a poorer survival rate than those treated for recurrence after radiotherapy. The 5-year tumour-specific survival rate for patients having primary surgery was 28 per cent and for those receiving salvage surgery 59 per cent. Cox's regression analysis confirms this finding, which is difficult to explain (*Table 3*). Patients who had primary radiotherapy were a selected group. At the time of presentation they had disease of lesser volume than those undergoing primary surgery. Following radiotherapy, recurrence at the primary site occurred after a median interval of 18 months; in the primary surgery group median survival was similar. Patients submitted for salvage surgery are therefore in a favourable prognostic group.

Postoperative radiotherapy may reduce recurrence rates after primary surgery, although in this series the reduction was not significant. No effect was seen on survival. El-Bedawi *et al.*[45], however, did find a significant reduction in failure rate above the clavicles and an increase in survival when comparing surgery alone to surgery plus postoperative radiotherapy. Arguably, any hypopharyngeal cancer big enough to warrant primary surgery should also be treated with postoperative irradiation. Radiotherapy did not adversely affect complication rates and, in particular, was not implicated in the development of postoperative stenosis.

Presently, for patients with small hypopharyngeal tumours and no neck node involvement, radiotherapy is the treatment of choice; for those with small primary tumours and node metastasis, radiotherapy and radical neck dissection are employed. For larger tumours, where some of the pharynx can be saved, total laryngectomy and partial pharyngectomy is indicated. For larger tumours that have not spread to the thoracic oesophagus, total pharyngolaryngectomy and repair with a free revascularized jejunal loop is the treatment of choice. If this is not feasible, oesophagectomy is also carried out, followed by gastric transposition. The mortality rate associated with the latter procedure is, however, high compared with that of jejunal loop repair[32,46].

Acknowledgements

The authors would like to thank Mrs Brenda Cowley for typing the manuscript and Mrs Tracey Whittle for technical assistance with the tables and figures. This project was funded by a grant from the North West Cancer Research Fund. The authors also thank Professor P. M. Stell, who built up the database and who also carried out many of the surgical procedures

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British Journal of Surgery 1996, 83, 1284–1287

Laparoscopic surgery for gastro-oesophageal reflux: beyond the learning curve

D. I. WATSON, G. G. JAMIESON, R. J. BAIGRIE, G. MATHEW, P. G. DEVITT, P. A. GAME and R. BRITTEN-JONES

The Royal Adelaide Centre for Endoscopic Surgery and University Department of Surgery, Royal Adelaide Hospital, Adelaide, South Australia 5000, Australia
Correspondence to: Mr D. I. Watson

From September 1991 to October 1995, 320 Nissen fundoplications were undertaken laparoscopically by 12 surgeons at a single institution. To assess the performance of the procedure in the hands of five 'experienced' surgeons, the first 20 procedures performed by each surgeon or surgical trainee were excluded, providing a group of 174 patients for review. A short loose 360° fundoplication was performed in all instances, with short gastric vessel division performed in 35·0 per cent of patients and hiatal repair in 66·7 per cent. Median operating time was 80 (range 30–210) min and median postoperative stay was 3 (range 1–19) days. Sixteen procedures (9·2 per cent) could not be completed laparoscopically and required conversion to open surgery. Some 144 patients were reviewed by a scientific officer 3 months after surgery, 85 at 12 months, and 32 at 2 years, using a standard clinical questionnaire. All but one were free from reflux symptoms, although 20·1 per cent reported some dysphagia at 3 months' follow-up; this figure declined to 11 per cent at 12 months and 6 per cent (two of 34 patients) at 2 years. At each follow-up interval, 91 per cent of patients were satisfied with the outcome of the surgery. Objective testing with oesophageal motility (75 patients) and barium swallow (113) studies 3–6 months after surgery confirmed the clinical outcome. Complications occurred in nine patients (5·2 per cent); four (2·3 per cent) of these required a subsequent operation within 30 days of surgery for bleeding (one patient), paraoesophageal herniation (one) and dysphagia (two). A further procedure was necessary in six other patients (3·4 per cent) for late problems, including paraoesophageal herniation (two), hiatal stenosis (three) and gastric obstruction (one). Revision was performed laparoscopically in two patients. The clinical results of laparoscopic Nissen fundoplication by 'experienced' laparoscopic surgeons were comparable with those of open surgery.

Since the initial description of laparoscopic antireflux surgery in 1991[1,2], experience and expertise have been acquired rapidly in many centres, with several reports now describing experience of more than 100 procedures[3–7]. It is too early to assess the long-term results, which will be essential to evaluate the laparoscopic approach to surgery for gastro-oesophageal reflux.

The introduction of laparoscopic fundoplication has not been without difficulties; a number of complications specific to this procedure have been described. Problems have included reoperation for troublesome dysphagia[6,8], early postoperative paraoesophageal hiatus herniation[9], fibrous stricturing of the oesophageal hiatus[10] and visceral perforation[1,6,11]. Some of these problems may have resulted from inexperience during the evolution of the laparoscopic procedure, whilst others may result from modifications to established techniques aimed at making the laparoscopic approach easier to perform. Two postoperative deaths have also been reported[7,12].

Earlier reports included the 'learning curve' experience of each contributing surgeon introducing a potential bias when making a comparative assessment with open techniques. The authors' early experience with laparoscopic fundoplication has been reported elsewhere[4,5]. This was associated with a 10 per cent rate of conversion to open surgery, as well as a significant reoperation rate. The experience involved a major learning and training component, as these procedures were performed by seven consultant surgeons and four surgical trainees. To determine whether results have improved with subsequent experience, overall outcome was evaluated after excluding all patients operated on by a surgeon during the learning curve. This defined a group of patients whose surgery was performed by experienced surgeons only.

Patients and methods

From September 1991 to October 1995, 320 patients underwent laparoscopic Nissen fundoplication by one of 12 surgeons and trainees associated with the Royal Adelaide Centre for Endoscopic Surgery. All patients admitted for antireflux surgery were offered the laparoscopic approach, irrespective of any difficulties perceived by preoperative assessment such as obesity, large hiatal hernia, previous upper abdominal surgery, oesophageal stricture or Barrett's oesophagus. Data on preoperative assessment and management, surgical procedure and postoperative outcome for each patient were collected prospectively and stored on a computerized data base (FileMaker Pro; Claris Corporation, Santa Clara, California, USA). Patients had preoperative oesophageal manometry, and objective evidence of gastro-oesophageal reflux was confirmed by endoscopy and/or pH monitoring.

Postoperative clinical follow-up was obtained by the application of a standard questionnaire administered by a non-clinical scientific officer 3 and 12 months after surgery, and then annually thereafter. The presence or absence of heartburn, liquid and solid food dysphagia, as well as patient satisfaction with the procedure was graded from 0 to 10 using visual analogue scales. The presence or absence of gas bloat, ability to burp and ability to relieve abdominal distension, as well as the patient's willingness to undergo the same procedure again under similar preoperative circumstances, were also determined. Details of adverse outcomes such as hospital readmission, complications or surgical revision were recorded. Between 3 and 6 months after

Paper accepted 4 December 1995

surgery patients were encouraged to have repeat oesophageal manometry with testing for acid reflux, and a barium swallow examination. Endoscopy was reserved for symptomatic patients with clinical indications.

It was estimated that a surgeon's learning curve should comprise 20 procedures. This number was selected as preliminary experience suggested that the learning phase for laparoscopic fundoplication was longer than that for laparoscopic cholecystectomy[13,14]. The first 20 patients operated on by each surgeon who contributed to the overall departmental experience were excluded. This left a group of patients whose surgery was performed by 'experienced' surgeons. Patients who underwent another laparoscopic prcocedure at the same time as fundoplication were excluded from analysis.

The surgical technique used has been described in detail previously[4]. Five trocars were sited following Veress needle insufflation at the left costal margin. Both pillars of the oesophageal hiatus were dissected initially to expose the distal oesophagus and enable posterior hiatal repair when appropriate. Short gastric vessels were divided between clips in some patients before construction of a short loose fundoplication, calibrated over a 52-Fr bougie within the lumen of the oesophagus. Three or four interrupted polypropylene sutures were used to secure a total fundoplication of about 2 cm in length.

Results

Of the 320 patients who underwent the laparoscopic Nissen procedure, 140 operations were performed by surgeons who had completed 20 or fewer procedures. A further four patients had cholecystectomy and two had highly selective vagotomy at the time of laparoscopic fundoplication. Thus, 174 patients were identified who had surgery by five 'experienced' surgeons. These surgeons had performed 102, 64, 51, 39 and 27 procedures in their individual experience. There were 103 men and 71 women. Median age was 48 (range 15–82) years and weight 80 (range 51–120) kg. A sliding hiatus hernia was demonstrated before operation in 88 patients (50·6 per cent). Fifty-four patients (31·0 per cent) had undergone previous open abdominal surgery of whom 22 (12·6) had had upper abdominal surgery.

A total of 158 procedures were completed laparoscopically, while 16 (9·2 per cent) required intraoperative conversion to open surgery because of difficulties with the laparoscopic approach (*Table 1*). Median operating time was 80 (range 30–210) min. Short gastric vessels were divided in 61 patients (35·0 per cent), and the hiatus was narrowed with sutures in 116 (66·7 per cent). Median postoperative hospital stay was 3 (range 1–19) days.

Complications occurred in nine patients (5·2 per cent) within 30 days of surgery (*Table 2*). No respiratory morbidity was seen. Severe dysphagia was managed successfully by endoscopic dilatation in two patients, endoscopic retrieval of a food bolus in one and reoperation in two. The food bolus obstruction was associated with early consumption of large pieces of unchewed meat, despite specific instructions on avoidance. Early reoperation within 30 days of the original procedure was necessary in four patients (2·3 per cent), for acute paraoesophageal herniation (one), bleeding from a short gastric vessel (one) and dysphagia (two; one operation was achieved laparoscopically on the second day after fundoplication by removal and replacement of a single 'tight' suture). A later surgical procedure was required for a further six patients (3·4 per cent), between 2 and 11 months after the original surgery: two for paraoesophageal herniation (one revised laparoscopically at 6 months), three for stricture of the diaphragmatic hiatus resulting in dysphagia in spite of a demonstrably loose fundoplication, and one for gastric obstruction due to a poorly constructed fundoplication. Each of these complications has been described in detail elsewhere[9,10].

Table 1 Reason for conversion to open surgery

	No. of patients
Obesity	5
Large hiatus hernia	4
Adhesions	3
Perioesophagitis	2
Liver hypertrophy	1
Bleeding	1

Table 2 Postoperative complications

	No. of patients
Dysphagia	5
Paraoesophageal herniation	1
Deep vein thrombosis	1
Bleeding short gastric vessel	1
Pneumothorax	1

Barium swallow examination 3–6 months after surgery in 113 patients (64·9 per cent) confirmed an intact fundoplication in all those examined. However, delayed emptying of barium through the fundoplication was seen in seven patients (6·2 per cent), a finding that correlated with postoperative dysphagia. This was associated with either a presumed tight fundoplication (four patients) or narrowing of the oesophageal hiatus (three). A small paraoesophageal hernia was noted in a further three patients. This was symptomatic in two, requiring late surgical revision, while the other patient remains symptom free.

Oesophageal motility studies confirmed correction of acid reflux in all 75 patients examined after operation, and a rise in resting lower oesophageal sphincter pressure from a median of 7 (range 1–44) mmHg before operation to 22 (range 4–70) mmHg after surgery. Incomplete lower oesophageal sphincter relaxation was more likely in patients with postoperative dysphagia. The clinical outcome in the subgroup of patients who had postoperative testing was similar to that of the remaining patients who did not undergo these tests.

Clinical follow-up of greater than 3 months was available for 144 patients (82·8 per cent). At 3 months, all but one were free from all reflux symptoms (99·3 per cent). However, 29 patients (20·1 per cent) described dysphagia for solid foods. Using a visual analogue scale from 0 (totally unsatisfied) to 10 (totally satisfied), 131 patients (91·0 per cent) rated the surgical outcome as 7 or better. A score of 7–10 approximated grades 1 and 2 of a modified Visick scale used in other studies in this department. Some 132 patients (91·7 per cent) expressed willingness to undergo the same procedure again under identical preoperative circumstances.

Of the 85 patients (48·9 per cent) who have been followed for more than 12 months, all but one (99 per cent) are free from reflux symptoms. Nine (11 per cent) report some dysphagia for solid food and 77 (91 per cent) rated the operation as 7 or better on the visual analogue scale of satisfaction. Thirty-two (18·4 per cent) of the patients have also been interviewed 2 years after surgery. Thirty-one are free from reflux symptoms, two continue to experience dysphagia for some solid foods and 29 are satisfied with the clinical outcome.

Discussion

Laparoscopic Nissen fundoplication is being used increasingly in the treatment of gastro-oesophageal reflux disease. As with laparoscopic cholecystectomy, it has been adopted rapidly by many surgeons who have been encouraged by the short-term reports published in the surgical literature. This published experience also suggests, however, that laparoscopic fundoplication is associated with a significant learning curve[3,4,7]. The technical challenge resulting from the inherent difficulties of a three-dimensional environment reduced to two planes, and the requirement for suturing, has contributed to a steep learning curve. All previous reports have contained this learning component, suggesting the possibility that the outcome from surgery performed by surgeons who have overcome the learning difficulties of the procedure may be better than earlier reports have suggested.

This paper describes the outcome in a large number of patients who had laparoscopic fundoplication by surgeons who had each performed at least 20 procedures previously. While surgeons may progress at different rates, it is believed that 20 cases is a conservative estimate of the learning curve and that learning-related difficulties have been eliminated in this study. In comparison with the authors' earlier experience[4,5], and that of others[3,7], laparoscopic fundoplication by experienced surgeons is associated with an improved outcome. The median operating time of 80 min compares favourably with that in all publications reporting more than 50 procedures[3–7] (*Table 3*), in which median operating times ranged from 110 to 150 min.

The 5 per cent complication rate is an improvement on the rate of 10 per cent reported by this group previously[5] and of up to 13 per cent reported by others [3–7,11,15] (*Table 3*). Of importance was a reduction in the incidence of postoperative paraoesophageal herniation and venous thromboembolism in this group of patients. The unusual problem of hiatal stenosis was still seen in this adjusted series, although the necessity for revision of the fundoplication for persistent dysphagia was uncommon (two patients). The early reoperation rate of 2·3 per cent, as well as the overall reoperation rate, declined from the rate reported earlier[5]. Although the complication and reoperation rates compare favourably with previously published experience of open Nissen fundoplication[16–19], the early reoperation rate may be higher for the laparoscopic procedure. It is unusual for reoperation to be required within 12 months of open fundoplication. On the other hand, follow-up of patients who had laparoscopic fundoplication in this institution has been much more intensive because of the great interest in the outcome of this new technique. Importantly, this follow-up was obtained by a non-clinical scientific officer rather than the operating surgeon or any other member of the hospital clinical staff.

Late follow-up of 85 patients reviewed 12 months after surgery, and of 32 patients reviewed at 2 years, has confirmed the durability of laparoscopic fundoplication as a treatment for symptomatic gastro-oesophageal reflux; very few patients developed further reflux symptoms. The incidence of solid food dysphagia declined with longer follow-up, and patient satisfaction remained at 91 per cent 1 and 2 years after surgery.

Several important lessons were learnt during early experience with laparoscopic fundoplication, leading to changes in surgical technique; these, along with improved surgical experience, may have contributed to the improved outcome. Failure to repair the diaphragmatic hiatus adequately, as well as perforation of the left pleural membrane at laparoscopic fundoplication, resulted in a high incidence of early postoperative paraoesophageal herniation[9]. The introduction of routine hiatal repair and improved hiatal dissection protecting the pleura reduced the incidence of this complication, although the rate may still be higher than that during open surgery.

Greater experience has also reduced operating times considerably, despite the addition of short gastric vessel division in 35 per cent of patients, compared with very few patients in the authors' initial learning period. It should be noted, however, that short gastric vessel division was performed in the context of a randomized trial, rather than because of a definite change in practice.

Is laparoscopic fundoplication justified? Patient morbidity is greatly reduced by the procedure; most patients return home in 3 days, and are back at work by 2 weeks. However, when does the disadvantage of a small early reoperation rate balance the advantage of reduced pain and early discharge? Long-term outcome 5–10 years after laparoscopic surgery will need to be as good as that reported after open surgery. These outcomes will remain unclear for several more years and, until they are known, the procedure must remain under evaluation. Potential difficulties during the learning phase, when surgeons begin to perform laparoscopic antireflux surgery, can be minimized by the provision of expert supervision. The time is probably right for trials to compare the laparoscopic technique with open surgery.

Table 3 Early outcome following laparoscopic fundoplication

Reference	Year	No. of patients	Conversion rate (%)	Operating time (min)	Complication rate (%)	Follow-up (months)	Symptomatic failure (%)
Cuschieri *et al.*[3]	1993	116	0·9	150 (mean)	13	13 (median)	8·6
Jamieson *et al*[4]	1994	155	12·3	120 (median)	9·7	9 (mean)	1·9
Weerts *et al.*[6]	1993	132	3·3	118 (mean)	7·5	3 (median)	1·1
Hinder *et al*[7]	1994	198	3·0	150 (median)	11·6	12 (median)	8·0
Cadiere *et al.*[11]	1994	80	4	150 (median)	9	3 (median)	0
Hallerback *et al.*[15]	1994	60	15	110 (median)	10	6 (approximate)	2

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British Journal of Surgery 1996, 83, 1288–1291

Impaired gut barrier function in malnourished patients

J. V. REYNOLDS, C. O'FARRELLY*, C. FEIGHERY*, P. MURCHAN,
N. LEONARD*, G. FULTON, C. O'MORAIN, F. B. V. KEANE and W. A. TANNER

*Departments of Surgery and Medicine, Meath and Adelaide Hospitals, Dublin, and Departments of Pathology and Immunology, *St James's Hospital, Leeds, UK and Trinity College Dublin, Ireland*
Correspondence to: Mr J. V. Reynolds, Academic Surgical Unit, St James's University Hospital, Leeds LS9 7TF, UK

The gastrointestinal tract is essential to host defence, acting as a barrier to absorption and translocation of gut antigens, including bacteria. In experimental models, protein malnutrition is permissive to gut barrier failure and endogenous infection. A clinical correlate has not been described. Intestinal morphology and barrier function to food protein antigens was studied in malnourished patients. Thirty-five individuals were evaluated, 20 malnourished patients and 15 well nourished hospital controls. Morphology was assessed from endoscopic biopsies of the second part of the duodenum, and serum immunoglobulin (Ig) G antibodies to gliadin and β-lactoglobulin were measured. No antibody to food proteins was evident in the control group. In contrast, serum IgG antibodies to at least one antigen were present in 15 malnourished patients and to both antigens in ten ($P < 0{\cdot}0001$ *versus* controls). Severely malnourished patients were more likely to have both antibodies present than those with mild or moderate malnutrition ($P < 0{\cdot}05$). Antibody-positive malnourished patients had significantly better nutritional status than antibody-negative patients with malnutrition ($P < 0{\cdot}05$). In no group of patients was there morphological evidence of abnormal mucosa or an immunological infiltrate. Gut barrier function is compromised in malnourished patients which suggests a mechanism that may facilitate gut-derived infection and sepsis.

The gastrointestinal mucosal barrier is central to host defence, excluding endogenous flora and toxins from the portal and systemic circulation. Failure of the gastrointestinal tract to act as an effective barrier may initiate or exacerbate sepsis in the surgical patient[1]. In the 'gut hypothesis' of sepsis and multiple organ failure, translocated enteric bacteria, in particular *Escherichia coli* and endotoxin, trigger widespread activation of pro-inflammatory cells with subsequent elaboration of cytokines which are the putative mediators of the metabolic, endocrine and neuroendocrine response[1]. The maintenance of gut barrier function is recognized as an important goal in the management of high-risk surgical patients and the critically ill[2,3]. The evidence from animal models is consistent but information on gut barrier function in relevant clinical situations is scant.

Malnutrition is prevalent in hospital patients and is associated with an enhanced risk of infection and sepsis[4,5]. The adverse effect of malnutrition on systemic immune function is well described[6–8]. Experimentally, malnutrition is associated with changes in the gastrointestinal tract, including intestinal weight loss out of proportion to weight loss in other viscera[9] and villus atrophy. The aims of this study were to determine whether malnourished patients have an altered immune response to dietary antigens, suggesting breakdown of normal antigen exclusion, and to assess the mucosa morphologically for signs of malnutrition, normally characterized by villus atrophy and absent brush borders[9].

Patients and methods

Ethical approval was obtained from the ethics committee of the Dublin Voluntary Hospitals. Thirty-five individuals were studied, 20 malnourished patients and 15 well nourished hospital controls. Protein malnutrition was defined by a score of 100 or less on the Nutrition Risk Index (NRI), calculated according to the following formula: 1·519 × serum albumin (g/l) + 0·417 × (current weight/usual weight) × 100. Malnutrition was further categorized as mild or borderline (NRI score 83·5–100) or severe (< 83·5) The methods used to develop these criteria have been described previously[10,11].

Following individual informed consent, endoscopic biopsies were obtained from the second part of the duodenum. All patients were feeding enterally before assessment, and none was avoiding wheat and milk. Patients receiving parenteral nutrition, those who had undergone operation, those with active peptic ulcer disease, inflammatory bowel disease, obstructive jaundice and acute pancreatitis, or on immunosuppressive medication, steroids and non-steroidal inflammatory drugs were excluded. Some 10 ml venous blood was taken and serum stored at −20°C for subsequent measurement of immunoglobulin (Ig) G antibodies to wheat (gliadin) and milk (β-lactoglobulin) protein.

Histopathology

Sections of small intestine were stained with haematoxylin and eosin. They were evaluated for villus height, crypt depth, villus area, brush border, lamina propria infiltrate and intraepithelial lymphocytes. The villus height was judged to be normal if the villus : crypt ratio was approximately 4 : 1. Ratios less than 3 : 1 were described as stubby. The number of intraepithelial lymphocytes per 300 epithelial cells was counted. Small intestinal morphology and immunocytochemistry were scored in a blinded fashion.

Detection of food antibodies to dietary protein

Enzyme-linked immunoabsorbent assays (ELISAs) for IgG antibodies to wheat and milk proteins were developed. Crude gliadin (Sigma Chemicals, Poole, UK) was dissolved in 0·1 ml acetic acid and β-lactoglobulin (Sigma) in carbonate–bicarbonate buffer. Microtitre plates coated with 100 μl of the antigen were stored overnight at 4°C, then washed four times with phosphate-buffered saline and 0·05 per cent Tween (PBS–Tween). Patients' sera and two reference sera (one positive and one negative) for each dietary antigen were added in 100 μl aliquots (in triplicate) at serial dilutions of 1/500, 1/1000 and 1/5000. Plates were incubated at 37°C for 40 min. The washing procedure was then repeated. Rabbit anti-human IgG conjugated with horseradish peroxidase diluted 1/1000 in PBS–Tween was applied at 100 μl

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Paper accepted 30 November 1995

per well. Orthopheylene diamine in phosphate–citrate buffer 0·1mmol/l pH 5 containing hydrogen peroxide was used as substrate for the conjugate, applied at 100 μl throughout. The plates were covered with tin foil and left at room temperature. The colour reaction was stopped at 8 and 10 min using 50 μl sulphuric acid 2·5 mol/l, and was measured immediately with an automated spectrophotometer at 490 nm.

To ensure reproducibility of the ELISA, quality control serum samples of known content were included with each plate. Optical density values of test sera were read from the reference curve obtained by serial dilution of the reference serum for each dietary antigen. This standard curve was then used to estimate the antibody level (in arbitrary units) of each test sample.

Initially, sera from a control group of 22 healthy individuals were tested to establish a cut-off point; 95 per cent of this group had antibody levels of less than 1 arbitrary unit for both β-lactoglobulin and gliadin. A level of more than 1 arbitrary unit was thus selected as a cut-off point, with more than 1 arbitrary unit being considered positive.

Statistical analysis

Data were expressed as mean(s.e.m.). Non-parametric analysis was done using the Mann–Whitney *U* test. Categorical variables were analysed by Fisher's exact test.

Results

Fifteen of 20 malnourished patients had cancer (upper gastrointestinal (eight), colorectal (two), pancreatic (two), renal (two) and melanoma (one)), compared with seven of 15 (five upper gastrointestinal, two colorectal) in the well nourished control group (*P* not significant). The five malnourished patients without cancer had chronic pulmonary disease (three), stroke (one) and short bowel syndrome (one). Of the eight remaining patients in the control group, four had chronic pulmonary disease, two non-specific abdominal pain and two benign biliary disease. Median (range) age in the well nourished group was 58 (34–78) years compared with 64 (33–80) years in the malnourished group (*P* not significant). Mean(s.e.m.) NRI score in the malnourished group was 86(3) compared with 106(3) in the control group ($P < 0{\cdot}0001$). The corresponding mean(s.e.m.) albumin levels were 34(3) and 41(3) g/l ($P < 0{\cdot}0001$).

Serum IgG antibodies to gliadin or β-lactoglobulin were negative in all control patients. In contrast, antibodies to β-lactoglobulin were detected in 15 of 20 malnourished patients, to gliadin in ten, and both antibodies were found in ten ($P < 0{\cdot}0001$ *versus* controls for each parameter). Mean(s.e.m.) IgG level in antibody-positive patients was 2(0·5) arbitrary units for gliadin and 5·6(3) arbitrary units for β-lactoglobulin.

Gastrointestinal morphology was normal in both groups. One severely malnourished patient had stubby villi. In no patient was there evidence of brush border deficiency or goblet cell deficiency. There was no significant difference in mean(s.e.m.) intraepithelial lymphocyte infiltrates between malnourished (35(5) per 300 epithelial cells) and control (31(4) per 300 cells) groups.

Significance of antibodies to food antigens in malnourished patients

The significance of IgG antibodies to gliadin and β-lactoglobulin was further evaluated by comparing the 15 malnourished patients who were positive for antibodies with the five who were negative, and the ten patients who expressed both antibodies with the five who were positive for just one. Mean(s.e.m.) NRI score was 84(2) g/l and mean(s.e.m.) albumin level was 33(2) g/l in the antibody-positive group compared with 93(3) and 37(2) g/l respectively in the antibody-negative group ($P < 0{\cdot}05$). The respective values for patients with antibodies to both antigens were 82(3) and 33(3) g/l compared with 86(3) and 34(1) g/l for the five patients who were positive for one antibody (*P* not significant).

The presence of one or both antibodies strongly correlated with the degree of malnutrition. Within the malnourished group, ten patients had severe malnutrition, defined as an NRI score less than 83·5, and ten had mild or moderate malnutrition. In the severely malnourished group, nine patients expressed one antibody, eight both and one neither. In the mild to moderately malnourished group, six patients were positive for one antibody, two for both and four were antibody negative. Only the presence of both antibodies correlated with the severity of malnutrition ($P < 0{\cdot}02$ Fisher's exact test). Age, the presence of cancer and the site of disease were not significant factors. Five of seven malnourished patients without gastrointestinal disease had antibodies to food antigens, compared with ten of 13 with gastrointestinal disease. The situation was similar for patients without cancer; four of five such malnourished patients had antibodies for β-lactoglobulin.

Discussion

In animal models, protein malnutrition is associated with villus atrophy[9], abnormal intestinal mucin[12], reduced secretory (s) IgA[13], impaired effectiveness of oral vaccines[14] and absorption of whole protein[15]. In children with kwashiorkor, reduced levels and affinity of s-IgA have been reported[16], as well as reduced efficacy of oral vaccines and decreased intraepithelial lymphocytes[17]. Small intestinal morphology is altered and increased transport of the macromolecular antigen horseradish peroxidase has been observed in biopsy specimens from malnourished children[18]. The importance of the findings in this study is that they occurred in a prevalent group of hospital patients rather than at the extremes of malnutrition induced experimentally or observed in kwashiorkor.

Raised levels of IgGs to food antigens were observed in the absence of any morphological change in small intestinal mucosa. There are several possible underlying mechanisms, both immunological and non-immunological. The normal response to an oral antigen in immune homeostasis is termed tolerance: a state of non-reactivity protecting the host from intestinal damage by inappropriate immune activity, and characterized by local generation of harmless specific s-IgA and an absent hypersensitivity response to the same antigen in the systemic circulation. Evidence of a specific immune response to dietary antigens in the circulation is rare, occurring in less than 10 per cent of healthy individuals[19]. Impaired oral tolerance, classically seen in gluten-sensitive enteropathy (coeliac disease), is associated with raised levels of serum IgG to dietary protein. Over 90 per cent of untreated, newly diagnosed patients with coeliac disease in this department have values of more than 1 arbitrary unit for both β-lactoglobulin and gliadin antibodies. In contrast to the present morphological findings in malnourished patients, coeliac disease is characterized by immunologically-mediated intestinal injury, with villus atrophy and an immunological infiltrate of predominantly intraepithelial lymphocytes. Although local immunological mechanisms were not studied in detail, the absence of villus atrophy and intraepithelial lymphocyte infiltrate in patients with serum antibodies to food proteins suggests that impaired antigen-specific tolerance to dietary antigens is not a key mechanism in malnourished patients.

A non-antigen-specific break in tolerance that occurs as a consequence of defective intestinal barrier function may be more likely. In normal circumstances, up to 0·01 per cent of ingested dietary protein is absorbed in adults[20]. This is increased, and is associated with the presence of antibodies to food antigens in conditions causing increased gut permeability, such as Crohn's disease[21]. Although it is conceivable that antibodies to dietary proteins in malnourished patients are generated by the mucosal immune system in response to luminal antigen, perhaps indicating a secondary response to earlier sensitization, it is more likely that an immunologically significant quantity of intact protein or identifiable peptide fragments has been absorbed. Increased absorption may occur in the presence of normal histology either through defective tight junctions (paracellular) or altered transport mechanisms (transcellular). The latter possibility is consistent with observations by Heyman *et al.*[18] in jejunal biopsy material from severely malnourished infants. Their studies suggested that augmented transcellular absorption of the horseradish peroxidase resulted from decreased intracellular processing. Absent or impaired production of IgA may be relevant to this process[20]. This is supported by studies in patients with s-IgA deficiency, a primary humoral immunodeficiency that is estimated to occur in up to 1 in 400 people. There are many similarities between s-IgA deficiency and malnutrition, including increased incidence of antibodies to food and bacterial antigens, increased susceptibility to infection, and normal mucosal morphology. It is possible that in malnutrition, as in s-IgA deficiency, the presence of several antibodies to food antigens in the absence of local intestinal immunopathology suggests that the active mechanism of tolerance mediated by suppressor T cells is bypassed, with consequent generation of antibodies against multiple food antigens.

What are the clinical implications? The contribution of infection of gut origin to the high risk of septic morbidity and mortality in malnourished patients is not defined. Experimentally, bacterial translocation and mortality from sepsis is enhanced in malnourished animals challenged with proinflammatory stimuli[22,23]. Bacterial adherence to mucosal epithelial cells is also increased in experimental models of malnutrition[24]. Patients who receive total enteral nutrition (TEN) following major surgery or trauma have fewer septic complications than those receiving total parenteral nutrition (TPN)[25]. TEN, which nourishes the gut, prevents gastrointestinal mucosal atrophy, attenuates the injury stress response, maintains immunocompetence and preserves normal gut flora[26,27]. Although a comparison of the benefit of TEN *versus* TPN based on preoperative nutritional status has not been performed, the differences may be further magnified if the gut mucosa is malnourished from the outset. These data suggest a fundamental impairment in gut barrier function is present in malnourished patients. The presence of antibodies correlated with the degree of malnutrition suggesting that the barrier defect becomes more generalized to a variety of antigens with progressive malnutrition. There was no specific correlation with the presence of cancer or gastrointestinal disease, suggesting that it is malnutrition *per se* rather than the disease which causes the alteration in barrier function. It is possible, however, that once initiated, barrier breakdown may be a factor promoting further malnutrition. If the 'gut-origin' theory of sepsis is valid, a compromised gut barrier may initiate or amplify significant sequelae following major surgery or septic challenge which may provide the pro-inflammatory cytokines to further impair local defences and mediate adverse clinical events. Efforts to replete gut mucosa nutritionally to restore gut barrier function and prevent further impairment in the postoperative period merit evaluation in malnourished patients. Specific evaluation of glutamine is merited, since recent studies have shown that glutamine added to TPN may reduce intestinal permeability and decrease septic complications[28,29].

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British Journal of Surgery 1996, 83, 1292–1299

British Association of Endocrine Surgeons Abstracts

Abstracts from the British Association of Endocrine Surgeons meeting held in Liverpool, UK, 17 May 1996.

Non-randomized comparative trial of open (posterior) adrenalectomy *versus* laparoscopic adrenalectomy

N. E. Dudley and B. J. Harrison, *Departments of Surgery, John Radcliffe Hospital, Oxford and Northern General Hospital, Sheffield, UK*

Between 1991 and 1993, 23 adrenalectomies were attempted by one of the authors who had not previously undertaken the Hugh Young posterior approach.

Between 1993 and 1996, 15 laparoscopic adrenalectomies were attempted by both authors working synchronously. Comparative data are presented regarding conversion rate, inpatient hospital stay, operating time, blood loss, morbidity and mortality.

	Open (posterior)	Laparoscopic
Conversion rate	1 of 23	3 of 15
Mean (range) operating time (min)		
Unilateral	85 (60–110)	193 (120–270)
Bilateral	119 (80–155)	386 (360–435)
Blood loss*	2 of 22	1 of 12
Morbidity		
Wound infection	1 of 22	1 of 12
Chest infection	1 of 22	0 of 12
Prolonged ileus	1 of 22	0 of 12
Other	4 of 22	1 of 12 (port-site hernia)
Perioperative mortality	0 of 23	1 of 15 (cause unknown)
Mean (range) inpatient stay (days)		
Unilateral	8·2 (7–11)	3·0 (2–4)
Bilateral	8·7 (7–11)	3·8 (3·5–4)
Mean (range) age (years)	41·6 (24–62)	29·9 (5–75)

*Required transfusion of 2 units blood

Traditional *versus* laparoscopic surgery in the treatment of phaeochromocytoma: a preliminary study

P. Miccoli, C. Bendinelli, G. Materazzi, P. Iacconi and P. Buccianti, *Dipartimento di Chirurgia, Universita di Pisa, Italy*

The laparoscopic approach for removal of phaeochromocytoma has been questioned Six laparoscopic adrenalectomies for phaeochromocytoma have been performed recently and the results are compared with those obtained using traditional open surgery

Between January 1988 and April 1995, 26 patients underwent surgery for phaeochromocytoma: 20 had an adrenalectomy through an upper abdominal transverse incision (group 1), and five unilateral and one bilateral laparoscopic adrenalectomy (group 2). There were 11 women in the first group and one in the second. Mean(s.d.) diameter of the mass was 5·8(5·8) and 5·3(2·1) cm respectively In both groups the right adrenal was affected twice as often as the left.

The following parameters were studied: operating time, hypertensive intraoperative crises, estimated blood loss, volume of liquid infused, day on which patients were back to semiliquid and full diets, complications and day of discharge. Mean follow-up was 56 months in group 1 and 10 months in group 2.

Mean operating times were 142 and 182 min in groups 1 and 2 respectively. In both groups, blood loss was similar: mean(s.d.) 311(40) ml in group 1 and 342(23) ml in group 2. Postoperative liquid infused was 9·6 litres in patients who had open surgery and 5·9 litres in those operated on with the laparoscopic approach, the largest difference in the liquid infused was observed after the first 24 h.

Patients operated on laparoscopically were discharged 3 days earlier In group 1 four patients developed fever and in two cases an infected wound was observed; one of them evolved into superficial dehiscence. The mean time elapsed to resume normal activity and return to work was reduced by 1 month in patients who underwent laparoscopic adrenalectomy.

Laparoscopic adrenalectomy: technical aspects based on a primary vascular dissection

J. Marescaux, D. Mutter and M. H. Wheeler*, *European Institute of Telesurgery (IRCAD-EITS) and University Department of Digestive and Endocrine Surgery, Hôpital Civil, Strasbourg, France and *Department of Surgery, University Hospital of Wales, Cardiff, UK*

This experience is based on 29 patients and observation of the technique of several pioneers (M. Gagner, L. Fernandez-Cruz, P. Miccoli). A technique using primitive vascular dissection ensures better adrenal and periglandular fat removal. The surgical procedure used a full lateral-decubitus and transperitoneal flank approach.

The key to successful left adrenalectomy is to start the procedure by dissecting the splenoparietal ligament close to the diaphragm to permit complete mobilization of the spleen to the right with the tail of the pancreas. Dissection of 5 cm of the splenic vein, used as a landmark, permits exposure of the renal vein which leads to the main and accessory adrenal veins. They can be divided safely between clips. The right side of the gland is dissected up to the diaphragm with clipping of the middle and upper arterial pedicles. Adrenalectomy is achieved by simple dissection of the fat. The gland is extracted though a bag.

The fundamental step of the right adrenalectomy procedure is sectioning of the hepatoparietal ligament far to the right allowing upward mobilization of the liver. The second step consists of dissecting towards the vena cava using this structure as a landmark to find the renal vein, which is the inferior limit of the dissection. The main adrenal vein is doubly clipped and divided. The third step is to look for an accessory adrenal vein joining a subhepatic vein above the main adrenal vein. The adrenal arteries are dissected on the right side of the vena cava. The last step is straightforward coagulation, vessel clipping and division, as on the left side

Indications for a laparoscopic approach in adrenal surgery

J. F. Henry, A. Denizot and M. Puccini, *Department of Endocrine Surgery, CHU la Timone, Marseille, France*

It has been demonstrated that the laparoscopic approach can be used safely and successfully in adrenal surgery. The aim of this study was to determine the indications for the laparoscopic approach in adrenal surgery.

Between June 1994 and November 1995, 56 patients underwent adrenalectomy for Conn's syndrome (23), Cushing's syndrome (ten), phaeochromocytoma (12), adrenocortical carcinoma (three) and incidentaloma (eight). A laparoscopic transabdominal flank approach was proposed in patients presenting with solitary or unilateral tumours measuring less than 8 cm in diameter, without suspicion of malignancy and without the usual contraindications to laparoscopic surgery.

Laparoscopic adrenalectomy was performed in 36 patients (64 per cent), with Conn's syndrome (20), Cushing's syndrome (eight), phaeochromocytoma (five) and incidentaloma (three). Mean size of the tumour was 26 (range 7–75) mm. Malignancy was demonstrated in two tumours. Four of 36 patients required laparotomy because of inadequate dissection (three) or operative suspicion of malignancy (one). Mean operating time was 159 (range 75–300) min. There were no deaths.

Postoperative complications were: bleeding from a trocar site (one), spleen infarction (one) and phlebitis (one). All patients with functioning tumours are disease free. The other 20 patients underwent open adrenalectomy. The laparoscopic approach was not recommended because of suspicion of malignancy (nine), previous surgery (seven), or bilateral or multiple tumours (four).

The laparoscopic approach is the procedure of choice in patients with functioning adenoma and sporadic unilateral intra-adrenal phaeochromocytoma. It may be discussed in patients with familial phaeochromocytoma. It is not indicated in patients with large (greater than 8–10 cm) or malignant tumours.

Benefits of routine laparotomy as the surgical approach for phaeochromocytoma and abdominal paraganglioma

C. A. G. Proye, F. N. Pattou, F. P. Combernale, B. Carnaille, X. Marchandise, M. Steinling, D. Huglo and C. L'Hermine, *Service de Chirurgie Generale et Endocrinienne, Centre Hospitalier Universitaire de Lille, Lille, France*

The records were studied of 100 patients who had undergone abdominal exploration and resection of at least one intra-abdominal phaeochromocytoma or paraganglioma over the past 17 years. Tumours were benign in 81 patients and malignant in 19 (nine locally invasive, seven with positive node(s), six with distant metastases), intra-adrenal in 83 patients (bilateral in 13) and extra-adrenal in 17, sporadic in 72 patients, and occurring in a genetic setting in 28. Abdominal (and possibly pelvic) computed tomography (CT), ^{131}I-*m*-iodobenzylguanidine (MIBG) scintigraphy and magnetic resonance imaging (MRI) had been performed since 1979, 1984 and 1987 in 97, 73 and 43 patients respectively. False-positive and false-negative results had been defined as any discrepancy between imaging result and surgical findings.

Imaging	*n*	False-positive (%)	False-negative (%)
CT	97	4	11
MIBG scintigraphy	73	7	16
MRI	43	5	9

Most of the inaccurate results were related to the localization of the tumour (either intra- or juxta-adrenal) or to the extent of periadrenal invasion. CT overlooked only two minute tumours in a familial setting of multicentric disease. MRI overlooked four tumours, including the two overlooked by CT. A striking feature was that all false-positive results of MIBG scintigraphy occurred in a genetic setting (four) or in teenagers (one). When the three techniques were combined in 38 patients, only one tumour, occurring in a bilateral and genetic setting, was overlooked.

The improved accuracy of available imaging techniques questions the strategy of routine laparotomy for sporadic phaeochromocytoma, favouring approaches such as the posterior or laparoscopic technique.

Clinical spectrum and outcome of functional extra-adrenal paraganglioma

D. S. O'Riordain, C. S. Grant, J. A. Carney and J. A. van Heerden, *Department of Surgery, Mayo Clinic and Foundation, Rochester, Minnesota, USA*

Functioning extra-adrenal paragangliomas represent over 10 per cent of all phaeochromocytomas, occur at diverse anatomical locations and are said to have a higher malignancy rate than intra-adrenal phaeochromocytomas.

Sixty-six patients had surgery for catecholamine-producing paraganglioma between 1952 and 1992. Median follow-up was 8·8 years. Median age was 40 (range 11–67) years; there were 29 men. Familial disease occurred in nine (14 per cent), and ten patients (15 per cent) also developed adrenal phaeochromocytoma.

Solitary paragangliomas occurred in 52 patients: 46 abdominal, four thoracic and two of the head and neck. Fifty-three tumours developed in 14 patients with multiple paragangliomas: 38 abdominal and 15 thoracic. Of 28 patients with solitary tumours undergoing localization studies in the past 10 years, accurate localization was achieved in 27. There was one operative death, 15 patients had persistent disease and 50 were cured. Of those cured, nine developed recurrence; disease-free survival rate was 86, 80 and 80 per cent at 5, 10 and 20 years respectively. Fourteen patients (21 per cent) had metastatic disease, of whom seven have died. An additional ten patients (15 per cent) had locally invasive disease, of whom four have died. Cause-specific survival rate at 5, 10 and 20 years was 90, 83 and 72 per cent respectively. Risk factors for death from phaeochromocytoma were tumour size greater than 5 cm ($P = 0{\cdot}0002$), metastatic disease ($P = 0{\cdot}001$) and tumour invasion ($P = 0{\cdot}002$). Cause-specific survival rate for patients with tumours greater than 5 cm was 59 per cent at 15 years compared with 100 per cent for those with tumours of 5 cm or less ($P = 0{\cdot}0003$).

Functional paragangliomas are frequently malignant and are associated with a high incidence of persistent or recurrent disease. Tumour size above 5 cm and the occurrence of invasive or metastatic disease are strong predictors of outcome. The majority of tumours are abdominal and imaging is highly successful in localization

Adrenalectomy in the treatment of Cushing's syndrome

S. Kocak, S. Ozbas, S. Aydrntug, S. Baskan and S. Eraslan, *Department of Surgery, Ankara University Medical School, Ankara, Turkey*

Trans-sphenoidal pituitary microsurgery is the treatment of choice in Cushing's disease but this treatment is not successful in all patients.

Between 1990 and 1995 nine patients with adrenocortical adenoma and 18 with bilateral adrenal hyperplasia were treated by adrenalectomy. All had complete symptomatic relief and there was no operative mortality or serious morbidity. Adrenalectomy should be the treatment of choice in patients with adrenocortical adenoma, and patients with Cushing's disease should be treated with bilateral adrenalectomy when pituitary surgery fails or cannot be performed.

Seven patients in this series had previously undergone trans-sphenoidal pituitary microsurgery; autonomous secretion of cortisol by the adrenocortical nodules was the cause of persistent disease in patients with nodular hyperplasia. Nodular adrenocortical hyperplasia may be a cause of persisting Cushing's syndrome following successful trans-sphenoidal pituitary surgery.

Adrenal autotransplantation may be carried out in patients with bilateral adrenalectomy to avoid lifelong replacement of steroids. The transplanted adrenal tissue should be stimulated by a cortisone-weaning process and autograft function should be determined by radioisotope scanning, not by hormone measurement.

Surgical strategy for organic hyperinsulinism

D. Simon, P. E. Goretzki and H.-D. Roher, *Department of Surgery, Heinrich Heine University, Dusseldorf, Germany*

Organic hyperinsulinism may be due to solitary or multifocal lesions, hereditary disease/multiple endocrine neoplasia (MEN) I, diffuse hyperplasia or malignancy. Precise biochemical diagnosis, standardized surgical exploration and consideration of distinctive features are essential for a successful surgical outcome. The necessity for preoperative and intraoperative localization techniques and management of multifocality and malignancy in organic hyperinsulinism remain controversial issues.

Between April 1986 and January 1996, 50 patients presented with organic hyperinsulinism. Forty patients had solitary adenomas, three multiple adenomas, two MEN I syndrome, one diffuse hyperplasia and four malignant insulinomas. Four patients underwent reoperation for recurrent disease (three with multiple adenomas, one with MEN I). Preoperative localization included abdominal ultrasonography, computed tomography, magnetic resonance imaging, endoscopic ultrasonography, angiography, octreotide scintigraphy and venous sampling. Preoperative localization was known and correct in 50 per cent of patients At operation, five tumours were not palpable; four of these could be detected by intraoperative ultrasonography. Mean size of the tumour was 16 (range 3–60) mm. Enucleation was performed in 28 patients (56 per cent), resection in 17 (34 per cent) (left resection 12, Whipple three, subtotal two), combined procedures in four (8 per cent) and hepatic resection in one patient.

Euglycaemia was achieved in 47 patients, including one with a two-stage operation after diagnosis of nesidioblastosis. All four patients with recurrence of disease had euglycaemia (three had multiple tumours and one MEN I; two underwent multiple enucleation and two resection) Three patients with malignant disease showed considerable improvement of symptoms. Two of these patients with symptomatic liver metastases were treated additionally by chemotherapy or chemoembolization.

It is concluded that (1) preoperative localization techniques do not influence surgical outcome and can be omitted; (2) intraoperative ultrasonography is indispensable for detection of small or multiple tumours; (3) patients with multiple tumours run a high risk of recurrence and so meticulous exploration with adequate resection or multiple enucleation is required; and (4) in malignant disease, radical removal of the primary lesion or tumour debulking can achieve relief from symptoms and potential cure

Laparoscopic treatment of insulinoma and gastrinoma

E. Cavina, P. Miccoli, P. Buccianti, P. Iacconi, O. Goletti, M. Chiarugi and M. Conte, *Dipartimento di Chirurgia, Universita degli Studi di Pisa, Italy*

This report describes two patients with pancreatic endocrine tumours successfully treated laparoscopically: a 23-year-old man with Zollinger–Ellison syndrome and a 47-year-old woman with an insulinoma. A precise biochemical diagnosis had been made and localization studies had determined the site of the tumours in the upper edge of the pancreas.

Patients underwent a traditional laparoscopic approach using four trocars in the first and five trocars in the second patient. Intraoperative ultrasonography was carried out to study the liver and pancreas through the stomach wall (7·5-MHz probe with flexible tip). In the first patient, a 2·2-cm extrapancreatic nodule contiguous to the upper border of the pancreas was visible through the lesser omentum; the echographic study was completed by endoscopic sonography of the pancreatic head and duodenum which confirmed the presence of a solitary nodule with no evidence of liver and lymph node metastases. In the second patient, a 2-cm tumour under the pancreatic body capsule was identified by intraoperative ultrasonography. Both tumours were resected, the second being enucleated from the pancreas by electrocautery and endoclips. Serum insulin and gastrin levels decreased after operation, confirming the radicality of the laparoscopic removal of the neoplasms. The patients were discharged after 2 and 4 days of an uneventful postoperative course.

Laparoscopic exploration and intraoperative ultrasonography might represent the first step in the surgical management of patients presenting with islet cell tumours.

Cytokines and neural cell adhesion molecule/CD 56 in the interaction between neuroendocrine tumours and natural killer cells

B. Wangberg, O. Nilsson, K. Hellstrand, G. Westberg and H. Ahlman, *Departments of Surgery, Pathology and Clinical Virology, Sahlgrenska University Hospital, Goteborg, Sweden*

Neural cell adhesion molecule (NCAM), or 56 DC, mediates both homophilic cell–cell interactions and heterophilic cell–matrix interactions Natural killer (NK) cells express CD 56 and are a subset of lymphocytes that kill tumour cells in a non-major histocompatibility complex-restricted fashion.

The occurrence of NCAM/CD 56 in neuroendocrine tumours was analysed by immunocytochemistry and Western blot analysis using the monoclonal antibody ERIC-1, which detects all four isoforms of NCAM/CD 56. Western blot analysis demonstrated a major 140-kDa band in foregut carcinoids (three of three), midgut carcinoids (14 of 15), islet cell tumours (four of four), phaeochromocytomas (ten of ten) and medullary thyroid carcinomas (five of five). Immunolabelling was confined to cell membranes of tumour cells, with no labelling over cytoplasm or nuclei. Primary cultures of midgut carcinoids (six of eight) also showed the strongest labelling at cell–cell contacts. NCAM/CD 56 could not be detected in any of 15 colonic cancers.

During embolization of carcinoid liver metastases, pronounced activation of the NK cell system occurs in patients with good clinical response, probably as a result of the release of tumour cell products (serotonin, cytokines) during ischaemia. The cytotoxic activity of NK cells exerted on such tumours in primary cell culture ($n=5$) could be enhanced by incubation with exogenous interleukin 2 (4–20-fold) or interferon α (3–14-fold).

NCAM/CD 56 was demonstrated in the majority of neuroendocrine tumours and may be important in the interaction between these tumour cells and the host immune system, possible enhancing NK cell antitumour activity together with cytokines.

Clinical localization of parathyroid glands using [^{11}C]methionine position emission tomography scans for repeat exploration parathyroidectomy

W. J. B. Smellie, G. J. R. Cook, I. Fogelman, M. N. Maisey and A. E. Young, *UMDS of Guy's and St Thomas's Hospitals, Clinical PET Centre and Directorate of Surgery, London, UK*

Preoperative assessment of the anatomical location of parathyroid glands is an advantage in patients who have persistent hypercalcaemia after neck exploration for hyperparathyroidism to assess whether the glands are in an abnormal position and to guide dissection in heavily scarred necks.

Fifteen patients with primary and five with tertiary hyperparathyroidism with between one and three previous surgical explorations were included. All [^{11}C]methionine position emission tomography (PET) scans were compared with technetium-99m MIBI ($n=16$) or thallium-201 ($n=4$) parathyroid scans. Surgery was subsequently performed in seven patients. Scans of the neck and mediastinum were obtained 15 min after administration of 370–540 MBq [^{11}C]methionine. A further ten patients without previous surgery were also studied.

In patients with previous surgery, scans showed an abnormality in 11 of 15 with primary hyperparathyroidism and in two of five with tertiary hyperparathyroidism. Corresponding technetium-99m MIBI scans were abnormal in three of 15 and two of five. In the four patients operated on for primary hyperparathyroidism, all four glands were correctly localized by PET. In the three patients operated on for tertiary hyperparathyroidism two of three glands were subsequently shown by surgery to have been correctly localized by PET. In one patient technetium-99m MIBI correctly localized the glands but PET did not.

In the eleven patients without previous operations, PET localized the glands correctly in seven of eight patients with primary hyperparathyroidism and in three of three with tertiary hyperparathryroidism. Technetium-99m MIBI correctly localized four of eight and one of three.

[^{11}C]methionine PET may offer an alternative method of preoperative localization in patients with hyperparathyroidism. Preoperative localization is not necessary in patients initially diagnosed with hyperparathyroidism but [^{11}C]methionine PET may be more sensitive in localizing glands in patients in whom previous surgery has been performed.

Sestamibi–technetium subtraction scintigraphy in primary hyperparathyroidism

S. E. Refsum, J. D. Laird, W. R. Ferguson and C. F. J. Russell, *Departments of Endocrine Surgery and Nuclear Medicine, Royal Victoria Hospital, Belfast, UK*

Successful preoperative localization of parathyroid adenomas by subtraction scintigraphy has been limited by the inability of thallium–technetium scanning to identify small tumours. With a view to improving the sensitivity of the investigation, the isotope sestamibi has been substituted for thallium and, since January 1993, sestamibi–technetium subtraction scintigraphy has been performed routinely in patients with proven primary hyperparathyroidism (HPT) before neck exploration.

Between 1 January 1993 and 31 July 1995, 67 patients had sestamibi scans before first-time cervical exploration for HPT. Five scans were technically unsatisfactory and records could not be retrieved for eight patients. Of the remaining 54 individuals, 44 had a positive scan (one focus of activity after subtraction) and ten scans were negative. At operation, 48 patients each had a solitary adenoma, four had multigland enlargement and one had a parathyroid carcinoma.

For 48 patients with adenoma the scan result was correlated with operative findings and tumour weight:

	Weight of adenoma		
	<0·5 g	0·5–1·0 g	>1·0 g
Scan result			
True positive	11 (69)	9 (75)	18 (95)
False positive	5 (31)	3 (25)	1 (5)

Values in parentheses are percentages. One adenoma was not weighed

Sensitivity of the scan for detecting solitary parathyroid adenoma was 81 per cent; false-negative rate was 19 per cent. Sestamibi–technetium subtraction scintigraphy successfully localizes a high proportion of adenomas in HPT.

Tetrofosmin–^{123}I subtraction scanning in preoperative parathyroid imaging

C. A. G. Proye, B. Carnaille, C. P. Oudar, M. Steinling, M. Lecomte and D. Huglo, *Service de Chirurgie Generale et Endocrinienne, Centre Hospitalier Universitaire de Lille, Lille, France*

Tetrofosmine (TTF) is a cardiac imaging agent that may serve as a new radiopharmaceutical for parathyroid scanning before surgical exploration in patients with primary hyperparathyroidism (HPT).

Forty-six patients with primary HPT had a TTF–^{123}I scan followed by bilateral surgical neck exploration; all enlarged glands were excised, regardless of scan results. For TTF–^{123}I parathyroid scanning, planar images of the neck and mediastinum were performed 20 min and 2 h after injection of 15 milliCi (555 MBq) TTF (1,2-bis[bis(2-ethoxyethyl)phosphoro] ethane; Myoview, Ametstam Laboratory). Then, 150 μCi (5·5 MBq) ^{123}I was injected. Planar images were performed 2 h afterwards and subtracted from TTF images.

Eucalcaemia was achieved in all patients after operation. During surgery, 174 parathyroid glands were identified including 58 enlarged ones (31 adenomas and 27 hyperplastic). HPT was uniglandular in 36 patients and multiglandular in ten. TTF–^{123}I scanning correctly detected 44 enlarged glands (sensitivity 76 per cent, specificity 100 per cent) weighing 70–17 000 mg but overlooked 14 enlarged glands (four adenomas and ten hyperplastic) weighing 50–638 mg. Among the overlooked glands, four weighed more than 100 mg. Among 36 patients with uniglandular disease only two scans were falsely negative, whereas among ten patients with multiglandular disease all enlarged glands were successfully imaged in two patients only. One of four mediastinal adenomas was overlooked. TTF–^{123}I scanning results were not significantly correlated with preoperative 1–84 parathyroid hormone levels.

TTF–^{123}I subtraction scanning is one more improvement in preoperative imaging of the parathyroid glands, occasionally detecting hyperplastic glands as small as 70 mg. It does not allow successful imaging of all enlarged glands in multiglandular disease and can overlook tiny mediastinal adenomas.

Health screening for primary hyperparathyroidism with serum calcium and parathyroid hormone values in menopausal women

E. Lundgren, J. Rastad, G. Akerstrom and S. Ljunghall*, *Departments of Surgery and *Internal Medicine, University Hospital, Uppsala, Sweden*

Primary hyperparathyroidism (HPT) was screened for during mammographic health control of 5202 women aged 55–75 years. Re-examination of individuals with a serum calcium level of 2·55 mmol l^{-1} or more substantiated primary HPT in 2·1 per cent of the population. Primary HPT was diagnosed in women lacking substantial renal impairment, lacking a family history of hypercalcaemia, and low urinary calcium excretion providing the presence of hypercalcaemia and intact serum parathyroid hormone (PTH) 25 ng l^{-1} or more (37 women), serum calcium 2·50–2·60 mmol l^{-1} and serum PTH 35 ng l^{-1} or more (55 women), or serum calcium below 2·50 mmol l^{-1} and serum PTH above the normal range (17 women). Serum calcium and PTH values were 2·32–3·19 (mean 2·59) mmol l^{-1} and 34–300 (mean 66·5) ng l^{-1} respectively. These values were positively correlated ($P=0·0001$) and were significantly higher ($P<0·0001$) than those in matched controls. Thirty patients demonstrated persistent normocalcaemia; all but two of them also showed consistently normal ionized plasma calcium concentrations. Within a stratified treatment programme, 60 of the patients have undergone parathyroid surgery with removal of pathological parathyroid tissue. This attempt systematically to explore and to verify diagnostic levels of serum PTH at operation in population-based health screening substantiates the considerable prevalence of primary HPT in menopausal women and suggests that criteria used for biochemical recognition may underdiagnose the disorder

Near-patient measurement of intact parathyroid hormone during parathyroidectomy

C. R. Squire, P. M. Hawksworth, S. V. Fox, P. Atkins* and W. D. Fraser, *Departments of Clinical Chemistry and *Surgery, Royal Liverpool University Hospital, Liverpool, UK*

Parathyroidectomy for parathyroid adenoma can be a difficult operation, especially if there has been previous surgery. Localization and confirmation of successful surgical removal of the adenoma can be assisted by parathyroid hormone (PTH) measurement in venous samples taken from the drainage area of the four glands, provided that timely results can be obtained.

A modified protocol for the Nichols Institute (Essex, UK) chemiluminometric assay for intact PTH was used and carried out in the theatre suite. Samples were collected into tubes containing ethylenediamine tetra-acetic acid and centrifuged at 13 000 r p.m. for 30 s in a microcentrifuge. The assay was carried out in duplicate according to the manufacturer's instructions except that samples were incubated for 10 min in a rotary incubating block at 50°C. A previously stored standard curve was used with two calibrators and two quality-control samples.

The time taken from receipt of the samples from theatre to reporting the results varied between 20 and 27 min, depending on the number of samples analysed

Intrabatch coefficient of variation was 10·5 per cent at 2·3 pmol l^{-1} and 5·8 per cent at 37·7 pmol l^{-1}. Interbatch coefficient of variation was 18·1 per cent at 3 7 pmol l^{-1} and 9·7 per cent at 18·1 pmol l^{-1}. Correlation between the rapid assay and routine immunoradiometric assay (Nichols Institute Intact PTH) was $y = 0\ 9x + 1\ 8$, $r = 9{\cdot}98$.

Using this method the location of an adenoma has been correctly identified and confirmed at successful removal in six patients.

Clinical and physiological responses to total parathyroidectomy after renal transplantation

T. J. Wheatley, T. M. Doughman, P. S. Veitch and M. L. Nicholson, *Department of Surgery, Leicester General Hospital, Leicester, UK*

Despite improvements in the medical management of secondary hyperparathyroidism, parathyroidectomy is still necessary in some renal transplant recipients. The operative strategy in this situation remains controversial Total parathyroidectomy has been criticized because of concern that the aparathyroid state will lead to adynamic bone disease and difficulties in therapeutic management

Total parathyroidectomy was carried out in a group of 21 patients with renal transplants. Total parathyroidectomy was performed in the 5-year period before renal transplantation (15 patients) or between 6 and 33 months after transplantation (six). Indications for surgery were severe bone disease (11 patients), uncontrolled hypercalcaemia (tertiary disease) (six), soft tissue calcification (one) and grossly raised parathyroid hormone (PTH) level (three). Surgery consisted of four-gland parathyroidectomy and included transcervical thymectomy where necessary.

The clinical and biochemical success rates at 24 months' follow-up were 87 and 100 per cent respectively Detailed skeletal surveys demonstrated evidence of partial or complete bone healing in 93 per cent of patients followed to 2 years. Postoperative PTH levels (measured by a sensitive immunoradiometric assay) demonstrated residual parathyroid function in 17 of 21 patients. At 2 years' follow-up there was only one patient with recurrent hypercalcaemia. Postoperative intravenous calcium infusion was necessary in 12 patients. Vitamin D analogues were required in 17. There was no recurrent laryngeal nerve palsy or permanent voice change after surgery. There has been no clinical evidence of adynamic bone disease and no therapeutic difficulty in any patient.

The data presented suggest that total parathyroidectomy is a safe and effective procedure in patients on dialysis who are awaiting a kidney transplant or in renal transplant recipients.

Fibroblast growth factors and receptor expression in proliferative disorders of the parathyroid

C. L. Eaton, D. L. Lambert and B. J. Harrison, *Department of Surgical Sciences, Clinical Sciences Centre, Northern General Hospital, Sheffield, UK*

The activities of polypeptide growth factors are important in the control of proliferation in glandular tissues. Previous studies have reported the presence of growth factors in abnormal parathyroid tissue. A basic fibroblast growth factor (FGF)-like factor is reported to be a potent mitogen for parathyroid tissue and may be implicated in the parathyroid disorder multiple endocrine neoplasia I.

The expression of acidic and basic FGFs and of FGF receptor (FGR-R) types 1 and 2 has been studied in human parathyroid tissue, utilizing Northern blot and reverse transcription–polymerase chain reaction (PCR) methodologies. To date RNA from seven adenomatous and 11 renal hyperplastic glands has been isolated. Comparison of the samples examined using primer pairs covering an extracellular domain of FGF-R types 1 and 2 has demonstrated the presence of transcripts for these genes in all samples. No gross difference in either PCR-amplified fragment size or level of expression was observed between glands from patients with primary and renal hyperparathyroidism. Detailed sequence analysis of PCR products and consideration of other primer pairs covering sequences encoding different functional domains of these receptors is currently ongoing.

Kindred with familial medullary thyroid carcinoma: expression of medullary thyroid carcinoma in heterozygous and homozygous disease gene carriers

C. Franz, J. Rice, H. Donis-Keller and S. A. Wells Jr (introduced by C. Proye), *Department of Surgery, University of Hamburg, Hamburg, Germany and Departments of Genetics, Psychiatry and Surgery, Washington University School of Medicine, St Louis, Missouri, USA, (Service de Chirurgie Generale et Endocrinienne, Centre Hospitalier Universitaire de Lille, Lille, France)*

Germline mutations in the *RET* proto-oncogene are associated with multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma (MTC). In a familial MTC kindred a novel point mutation in *RET* (codon 804 Val to Met) was identified and several individuals were homozygous for this mutation.

The expression of MTC in homozygous and heterozygous disease gene carriers was compared. Mutation analysis of 74 family members revealed 47 (16 homozygous and 31 heterozygous) disease gene carriers and 27 non-carriers. Ten of 31 heterozygous carriers and 15 of 16 homozygous carriers had disease. In unaffected carriers median age was 38 (range 24–69) years. Using survival analysis technique, age at diagnosis was significantly earlier in homozygous carriers ($P = 0{\cdot}002$, Wilcoxon test). Median age in the homozygous and heterozygous carriers was 49 and 60 years respectively. Preoperative stimulated calcitonin levels were higher in homozygous carriers, and lymph node metastasis (four individuals), persistent disease (three) and recurrent (two) disease occurred only in homozygous carriers. Expression of MTC is more apparent in homozygous disease gene carriers.

Medullary thyroid carcinoma in Northern Ireland

S. J. Dolan and C. F. J. Russell, *Department of Endocrine Surgery, Royal Victoria Hospital, Belfast, UK*

Medullary thyroid carcinoma (MTC) remains a rare malignancy. Between 1960 and 1995, 33 patients with MTC were treated at this hospital. Twenty-one patients had sporadic tumour; the remaining 12 had MTC as one component of multiple endocrine neoplasia (MEN) type 2A (ten patients) or type 2B (two) syndrome. All 33 individuals had histologically proven invasive carcinoma. Twelve patients (ten with sporadic tumour, two with MEN) had undergone thyroidectomy at other hospitals, although none had had total thyroidectomy.

Median age at presentation was 40·5 years for patients with sporadic tumour and 28·5 years for patients with MEN 2A. Clinically, 20 of the former patients and seven of those with MEN 2A had palpable goitres while ten and one respectively had cervical lymphadenopathy. One patient with MEN 2A had raised plasma calcitonin levels in the absence of clinical disease. Recently, a 10-year-old girl with MEN 2A underwent total thyroidectomy on the basis of positive genetic information alone.

Crude 5-year survival rate was 30 per cent for patients with sporadic MTC and 60 per cent for the MEN 2A group. Of the patients with sporadic tumour, 17 or 21 are dead (mean survival 61·2 months); seven of the ten patients with MEN 2A remain alive between 1 and 16 years (mean 104 months) after operation.

Improved survival in the MEN 2A setting may reflect a combination of biological behaviour of tumour, earlier diagnosis, less advanced disease and appropriate radical surgery.

Early diagnosis of sporadic medullary thyroid carcinoma by routine measurement of serum calcitonin levels

M. Puccini, P. Miccoli, A. Denizot, C. de Micco, B. Conte-Devolx and J. F. Henry, *Department of Endocrine Surgery, CHU la Timone, Marseille, France*

Sporadic medullary thyroid carcinoma (MTC) has a significant associated mortality rate. The 10-year survival rate is around 60 per cent. It may be expected that diagnosis and treatment at an early stage will improve prognosis This study assessed the diagnostic accuracy of serum calcitonin (CT) measurement in detecting sporadic MTC in patients with thyroid disease.

Between 1993 and 1995, 2974 patients presenting with thyroid disease had basal CT measurement (Elsa-h CT kit, CIS-Bio industries, normal level less than 10 pg ml^{-1}). When serum basal CT level was above the normal range, a pentagastrin stimulation test was performed (normal value less than 30 pg ml^{-1}). Sporadic MTC was suspected in patients with a CT peak above 100 pg ml^{-1}. Clinical solitary or dominant nodules were assessed by fine-needle aspiration cytology (FNAC). No patient had a history of familial MTC or multiple endocrine neoplasia II.

In 13 patients (0·4 per cent) sporadic MTC was diagnosed. In eight patients (group 1) diagnosis was made both by FNAC and CT measurement but in five patients initial cytological diagnosis was incorrect: anaplastic (two), papillary (two), benign (one). A revised cytological diagnosis of sporadic MTC was made after detecting raised serum CT concentration. In the last five patients (group 2) sporadic MTC was not detected clinically and FNAC was not performed. Sporadic MTC was diagnosed before operation by raised serum CT level alone. In this group mean size of the tumour was 6 (range 1·2–9) mm and there was no lymph node involvement. After surgery, only four of the eight patients in group 1, but all five patients in group 2, had a normal CT concentration.

Routine measurement of serum CT improves the preoperative diagnosis of sporadic MTC and allows early diagnosis of occult tumours.

Familial papillary carcinoma of the thyroid

J.-L. Kraimps, R. Marechaud and J. Barbier (introduced by C. Russell and B. Carnaille), *Department of Surgery, Jean Bernard Hospital, Poitiers, France*

Papillary thyroid carcinoma (PTC) is usually sporadic but may be familial. The relative frequency of familial *versus* sporadic papillary carcinoma is uncertain. Autosomal dominant inheritance with incomplete penetrance is possible. This study examined 15 patients with familial PTC and attempted to define a diagnostic and therapeutic approach.

During the past 5 years, familial occurrence of PTC was observed in 11 patients from seven families. Questioning these patients revealed four other individuals with PTC in their family. Where familial occurrence was indicated by the patient, attempts were made to obtain pathology reports to confirm the diagnosis. A complete pedigree was obtained. Statistical analysis was based on corrected χ^2 test with Yates' correction.

Within these seven families, 28 patients had a nodular goitre and 24 underwent surgery. Nine had a multinodular goitre and 15 had PTC. During the same time, 105 patients with PTC were operated on, with a 10·5 per cent rate of familial PTC. There were ten women and five men, with two affected relatives in six families and three in one family. Mean age was 33 (range 11–66) years. The relationship between patients was 'parent and child' in three families, 'siblings' in two families and 'cousin' in two families. PTC was multifocal in seven of 15 patients *versus* 22 (23 per cent) of 94 patients with sporadic PTC treated in the same time. This difference, however, was not significant.

It can be concluded that (1) about 10 per cent of all patients with PTC may have an affected relative; (2) when two or more patients in a family have PTC, all first- and second-degree relatives should be considered at risk; and (3) the disease appears to be frequently multifocal.

Thyroid gland volume in patients with breast cancer

S. G. Shering, A. P. Zbar, E. W. M. McDermott, P. P. A. Smyth and N. J. O'Higgins, *Departments of Surgery and of Medicine and Therapeutics, University College Dublin, St Vincent's Hospital, Dublin, Ireland*

The prevalence of non-toxic goitre and of asymptomatic thyroid gland enlargement (as determined by high-resolution ultrasonography) is significantly greater in patients with breast cancer than in age-matched controls. The significance of this observation is unknown. This study examined the relationship between thyroid volume and tumour characteristics in patients with breast cancer.

Thyroid volume was determined by high-resolution ultrasonography in 245 patients with a histological diagnosis of breast cancer over a 5-year period (1988–1993). All measurements were performed by one operator using a scanner fitted with a hand-held 7·5-mHz linear transducer. The volume of each thyroid lobe was calculated using the formula width × depth × length × 0·479.

Thyroid volumes were significantly greater in patients with axillary node-negative cancers ($P = 0{\cdot}04$, Mann–Whitney *U* test), larger breast tumours ($P = 0{\cdot}032$, Kruskal–Wallis test) and oestrogen receptor-positive tumours ($P = 0{\cdot}028$, Mann–Whitney *U* test). There was no clear association between thyroid volume and histological type or grade of the breast tumour. Patients with very large thyroid glands (greater than 30 ml) and very small thyroid glands (10 ml or less) had a significantly better outcome in terms of both disease-free ($P = 0{\cdot}005$, log rank test) and overall ($P = 0{\cdot}011$, log rank test) survival after a median follow-up of 4·6 years. Using the Cox proportional hazards model, thyroid volume was an independent prognostic factor when the effects of nodal status, tumour size and oestrogen receptor status were considered.

These findings have stimulated a search for factors that affect both thyroid volume and breast cancer progression.

Surgical goitres in adolescence and childhood: an update and audit

A. J. Webb, *Department of Surgery, The Royal Infirmary, Bristol, UK*

A series of young patients (up to and including 16 years of age) was presented to the Association in May 1990. It has been updated to cover the period 1967–1994 and now comprises 17 patients and 18 goitres. All have been studied in detail and the performance, at all stages, audited.

Some 20 surgical operations, including eight lobectomies and two near-total thyroidectomies, were carried out. The benign lesions included nodular goitre (four), non-toxic hyperplasia (three) and chronic lymphocytic thyroiditis (three). There were five neoplasms, namely follicular adenoma (three) and papillary carcinoma (two).

Significant problems in diagnosis, management or interpretation of histopathology arose in 12 of 17 patients.

Because of the rarity of goitres, and particularly neoplasms, in this age group and the reasonable assumption that no single centre in the UK will collect a sizeable series, some tentative conclusions from this audit are offered.

1. A standard and invariable investigation schedule should include ultrasonography and fine-needle cytology.
2. Clinical awareness of all goitres is necessary, but especially the possibility of non-toxic hyperplasia and chronic lymphocytic thyroiditis.
3. A surgical strategy for papillary carcinoma is required taking into account the variation in biological behaviour.
4. Joint management between paediatric oncologists and endocrine surgeons is necessary.

Thyrotoxicosis during pregnancy

A. Ghanaiem and P. Atkins, *Department of Surgery, Royal Liverpool University Hospital, Liverpool, UK*

Twenty pregnant patients with thyrotoxicosis were managed by rendering them euthyroid with antithyroid drugs and performing bilateral subtotal thyroidectomy during the middle trimester.

All patients delivered normal babies. There has been no recurrence of thyrotoxicosis over a mean follow-up of 7 years. After surgery, all patients were treated with thyroxine until after delivery, when it was withdrawn. Four patients have subsequently needed long-term thyroxine. No patient had recurrent laryngeal nerve injury. Two patients were hypocalcaemic after surgery and one remains on calcium supplements 8 months after surgery.

Subtotal thyroidectomy remains an attractive form of treatment for thyrotoxicosis in pregnancy; the thyrotoxicosis is rapidly cured and normal pregnancy and delivery ensue.

Initial experience of the NIM 2 nerve integrity monitor in thyroid and parathyroid surgery

J. Barwell, D. Wilkins, J. Little and R. Page, *Department of Surgery, Derriford Hospital, Plymouth, UK*

The efficacy of the nerve integrity monitor (NIM 2), as perceived by the operating surgeons, in protecting the recurrent laryngeal nerve during thyroid and parathyroid surgery was assessed. Changes in surgical, anaesthetic and theatre staff practices that are necessary in implementing its use were evaluated.

Fifteen recurrent laryngeal nerves in 11 patients were dissected by three surgeons during operations in a general surgical service setting. Using a pro forma, surgeons were asked to score (on a scale of 1 to 10) their assessment of the help provided by the nerve integrity monitor during various parts of the operation. Anaesthetic staff were asked to comment on any variations imposed on their first choice of anaesthetic and delays that resulted Increases in theatre staff workload were also recorded for each patient. A clinical assessment of preoperative and postoperative (immediate and 6-week) vocal cord function was made.

Thirteen of the 15 nerves were successfully identified by the integrity monitor. Faulty endotracheal tube electrodes were the cause of failure in one patient. In the other, a parathyroid adenoma was found lying in a superficial position and dissection of the nerve, therefore, did not proceed. In the 13 completed patients, surgeons scored a mean of 8·6 for help in confirming visualization of the nerve and 9·1 for help in demonstrating an intact nerve at the end of the procedure. However, a mean score of only 2·9 was given for help in identifying the nerve before visualization.

Induction of anaesthesia was increased by an average of 10 min and a mean of 38 min of extra theatre staff time was associated with each patient on whom the monitor was used. The main anaesthetic problems reported were that the purpose-built endotracheal tube was too soft, permitting kinking and obstruction. The positioning marks on the tube were not clearly visible. Some anaesthetists considered it a disadvantage that paralysing agents could not be used during the procedure. Not surprisingly in this small study, no recurrent laryngeal nerve damage was suspected on clinical findings after operation

The integrity monitor effectively demonstrates an intact recurrent laryngeal nerve at the end of surgery (possibly of medicolegal significance). It does not help the surgeon in actually finding the nerve. Confirmation of the visualized nerve by the integrity monitor, while reassuring, cannot remove the risk to its branches (which occur in 58 per cent of specimens) during further dissection. For routine thyroid and parathyroid surgery, the NIM 2 nerve integrity monitor should be regarded as a medicolegal aid rather than a surgical tool.

Examination of vocal cords by videolaryngostroboscopy before and after thyroid operations

S. Kocak, I. Kocak, S. Ozbas, S. Aydintug and S. Baskan, *Departments of Surgery and Ear, Nose and Throat, Ankara University Medical School, Ankara, Turkey*

Vocal cord paralysis is one of the most serious complications of thyroid surgery. Routine dissection and demonstration of the recurrent nerve is controversial. The superior laryngeal nerve should be preserved by careful dissection and ligation of the branches of the superior thyroid vessels. The reported rate of primary recurrent nerve paralysis with the visualization method is about 3 per cent. The palsy is permanent in one-third. Indirect laryngoscopy is not sufficient to differentiate temporary from permanent paralysis. Injuries to the external branch of the superior laryngeal nerve are not easily diagnosed when examination of the vocal cords is performed by indirect laryngoscopy.

Indirect laryngoscopy and videolaryngostroboscopy (VLS) were performed in 108 patients before and after thyroidectomy as a prospective study. Nine patients developed voice disturbance after operation, which was permanent in one. VLS was carried out in another 18 patients with hoarseness after thyroidectomy, who were not evaluated before operation.

Superior and inferior laryngeal nerve injuries, laryngeal injuries due to endotracheal intubation and other laryngeal disturbances were differentiated by VLS but rarely by indirect laryngoscopy. VLS was also successful in diagnosing temporary and permanent vocal cord paralysis.

VLS should be performed in patients with voice disturbance after thyroidectomy.

Management of thyroglossal cyst

A. Ghanaiem and P. Atkins, *Department of Surgery, Royal Liverpool University Hospital, Liverpool, UK*

Diagnosis of thyroglossal cyst was made in 30 patients. Ultrasonography was undertaken in 21 and technetium scan in 12.

The findings at operation and subsequent histological analysis confirmed the diagnosis of thyroglossal cyst in 28 patients. Two patients had thyroid adenoma; both lesions had been shown on ultrasonography to be partly cystic.

One patient with a thyroglossal cyst was shown to have a papillary carcinoma in the wall of the cyst. Sistrunk's procedure was undertaken in all but two patients. The patient with a papillary carcinoma subsequently underwent total thyroidectomy and foci of carcinoma were found in both lobes.

Surgery was complicated by postoperative haemorrhage in one patient and a thyroglossal fistula recurred in one patient with a thyroglossal cyst in whom Sistrunk's procedure was not undertaken.

Surgery for thyroglossal cyst should always include removal of the middle of the hyoid bone but Sistrunk's procedure may not be adequate treatment if the cyst wall contains a papillary carcinoma.

British Journal of Surgery 1996, 83, 1300–1306

Correspondence

Randomized comparison of agents for caudal anaesthesia in anal surgery

Sir

In their Short Note (*Br J Surg* 1996; 83: 364–5), Dr Adebamowo and his colleagues suggested that caudal epidural anaesthesia using 2 per cent lignocaine with 1 : 100 000 adrenaline produced adequate sensory block of faster onset and longer duration than that with 2 per cent lignocaine plain or 1 per cent lignocaine with 1 : 100 000 adrenaline These observations are not new While the present findings are accepted tenets in regional anaesthesia[1–3], we believe their data do not support this conclusion

The primary mechanism of caudal epidural anaesthesia is spinal root block Local anaesthetic injected into the caudal space must diffuse across the meningeal barrier (dura) before conduction block is possible. Clearly, the more concentrated the local anaesthetic solution, the steeper the diffusion gradient and the faster the onset time. Similarly, concentrated local anaesthetic solution delays the reversal of the gradient and the longer the block lasts. However, dural transfer of anaesthetic molecules is also a function of the caudal epidural anaesthetic mass (i.e. total dosage)[4]. Hence, it is not surprising, for example, that prilocaine given epidurally either as 30 ml 2 per cent solution or as 20 ml 3 per cent solution failed to demonstrate any significant difference in onset time or duration of anaesthesia[5]. Therefore, while the volume of caudal injection is not known in this study, we believe it is impossible to interpret the present data. A proper experiment comparing local anaesthetic solutions of different concentrations should keep the total dosage constant.

With regard to the role of caudal adrenaline, it is now well established that the minimal effective concentration for its use in epidural anaesthesia is about 2·5 μg/ml (1 : 400 000). It appears that increasing the dose beyond 5 μg/ml (1 : 200 000) provides no additional benefit[6]. While most adult caudal injection for anal surgery requires a volume of 20–30 ml, we are concerned that local anaesthetic solution with adrenaline 10 μg/ml (1 : 100 000) is potentially dangerous and increases the likelihood of side-effects.

Despite the reported complications, we are most impressed with the authors' results. We are also encouraged by the fact that non-anaesthetists have taken interest in regional anaesthesia. However, we wish to stress that major regional anaesthesia could produce important physiological changes and local anaesthetic toxicity, thereby contributing to patient morbidity and mortality. It is our policy to prevent any person from assuming dual responsibility as both the surgeon and the proceduralist[7]. It is important that during any form of major regional anaesthesia, a qualified person dedicated to patient monitoring and resuscitation must be present throughout the procedure and until the potential for local anaesthetic toxicity has passed.

M. T. V. Chan
K. K. Lam*

Department of Anaesthesia and Intensive Care
Chinese University of Hong Kong
Prince of Wales Hospital
Shatin
New Territories
Hong Kong
and
**Department of Anaesthesia and Intensive Care*
Tuen Mun Hospital
Tuen Mun
New Territories
Hong Kong

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Author's reply

Sir

We thank Drs Chan and Lam for their interest in our paper. The dose of local anaesthetic solution was indeed constant at 2 mg/kg – this fact was inadvertently omitted during the editorial process.

The choice of agents used was based on readily available preparations to avoid non-availability being used as a reason for non-use of this technique. Dilution of the 2 per cent lignocaine with 1 : 100 000 adrenaline to give 1 per cent with 1 : 200 000 is what we now use for our study, which is still continuing; results so far are satisfactory.

Our aim is to popularize a simple and economical technique associated with low morbidity and mortality rates in answer to a call for the same[1]. It is our belief that the technique will also be useful in those parts of the world where anaesthetists are still a luxury[2]. We certainly agree with Drs Chan and Lam that the results are impressive and this should encourage wide adoption of the technique.

C. A. Adebamowo

Department of Surgery
University College Hospital
Ibadan
Nigeria

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Laparotomy for abdominal sepsis in the critically ill

Sir

We read with interest the article written by Mr Anderson and his colleagues (*Br J Surg* 1996; **83**: 535–9). The authors have presented a large number of severely ill patients: the APACHE (Acute Physiology and Chronic Health Evaluation) II scores averaged 24, which is considerably higher than those mentioned in comparable studies documenting the severity of disease. Although Anderson *et al.* promised alternative approaches, they categorically abandoned the concept of relaparotomy on demand, although this retains its original advantages.

Our own studies and those of others[1–3] have shown that the mortality rate following relaparotomy on demand is higher than that associated with planned relaparotomy because of the delay. The only clear-cut indication for relaparotomy is multiple organ system failure (MOSF), but the decision to perform a relaparotomy must be made as soon as possible and certainly before MOSF becomes evident[1].

Recently Hau *et al.*[4] achieved significantly better results in patients treated by relaparotomy on demand *versus* planned relaparotomy regarding postoperative MOSF and infectious complications. Surgical treatment of abdominal sepsis is like finding the passage between Scylla and Charybdis. On the one hand it is important to do as little as possible, on the other hand it is essential to find out whether the patients are prone to persisting abdominal infection in spite of surgical cleansing at the initial operation. These patients are immunologically impaired because of initially high APACHE II scores, delay in diagnosing peritonitis or advanced age (more than 70 years). The relatively small proportion of patients in whom the source of infection was eradicated (62 per cent) can be explained by the fact that 66 per cent of patients in the study of Anderson *et al.* fulfilled the above mentioned criteria. This connection underlines the importance of defining patients who will not profit from initial surgical sanitation because of immunological impairment. That would help to reduce the interval before further operation.

The therapeutic use of planned laparotomies was selected in our department for patients with a source of infection that cannot be eradicated at initial operation. However, because we were not able to define immunologically impaired patients early in the course of disease, we used relaparotomies on demand in patients in whom initial operation had successfully eradicated the source of infection. The decision to perform a relaparotomy was made if there was no clinical improvement within the first 48 h, or if there was clinical deterioration.

In summary, we think that a prospective trial among patients with severe abdominal sepsis as requested by Anderson *et al.* is neither justified nor feasible.

T. Koperna
F. Schulz

Department of General Surgery
Hospital Lainz
Wolkersbergenstrasse 1
A-1130 Vienna
Austria

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Author's reply

Sir

We thank Drs Koperna and Schulz for their comments Interpreting the available literature is difficult because of lack of comparative studies, and international differences in both practice and disease severity among patients admitted to intensive care units. We would agree that the patients studied in our series were at least as old and as sick as any reported elsewhere, and this fact undoubtedly contributed to the high mortality rate. We cannot agree, however, that we advocated the wholesale abandonment of the laparotomy-on-demand approach. We simply pointed out that within our practice this approach is inevitably associated with some delay in the diagnosis of further or continuing abdominal sepsis, and that inadequate treatment of this is almost always fatal.

The question we seek to address is whether more aggressive surgical intervention can improve outcome. As we indicated in the paper, several subgroups of patients emerge in whom overwhelming clinical factors will be the principal determinant of outcome, almost irrespective of the treatment course followed. Thus, there exists a group of some 18 per cent who are too elderly and frail to survive the disease process even in the face of 'successful' surgical and intensive care treatment. There is a group of predominantly elderly and acutely unwell patients (mean APACHE II score of more than 29), the majority of whom pursue a remorseless, downward path and who are also unlikely to respond to any currently available therapy. These patient groups will overlap those with organ failure, some of whom have continuing abdominal sepsis, and among these will be patients with severe immunological impairment as alluded to, but not defined by, Drs Koperna and Schulz. The literature does not indicate the optimal means of surgical treatment for those with continuing abdominal sepsis, although some form of improved abdominal cleansing is necessary. The study reported by Hau *et al.*[1] showed a higher mortality rate in patients undergoing planned relaparotomy when compared with those being treated by laparotomy on demand, but it is relevant that the mean age and mean APACHE score were significantly lower than those of our own patients. Furthermore, given that Hau *et al.* achieved clearance of sepsis in more than 90 per cent of their patients subsequently treated by relaparotomy on demand, one has to wonder what they hoped a further operation would achieve. The same message expounding the risks of surgical over-treatment among critically ill patients by an alternative technique, namely laparostomy, was highlighted by our department some 10 years ago[2].

Given that our surgical treatment of these patients is not perfect and that inadequate treatment is fatal, it seems sensible to mount a comparative investigation to try to identify a path forward. We are under no illusions as to the difficulty of this task, the large number of confounding factors, the explicit need for targeting any further operation on the appropriate patient group, and the relatively modest impact on overall survival that one could hope to achieve.

Possible entry criteria could include incomplete abdominal cleansing at first operation, APACHE score more than 20, delayed diagnosis (over 48 h) of generalized peritonitis and presence of multiple organ failure. One, or at most two, further lavages could be supported.

I. D. Anderson

Department of Surgery
Clinical Sciences Building
Hope Hospital
Salford M6 8HD
UK

1 Hau T, Ohmann C, Wolmershauser A, Wacha H, Yang Q. Planned relaparotomy *versus* relaparotomy on demand in the treatment of intra-abdominal infections. *Arch Surg* 1995; 130: 1193–7.
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A better bridge for loop stomas

Sir

We were interested to read the Surgical Workshop by Mr Cochrane and colleagues (*Br J Surg* 1996; 83: 365). We favour the use of a Convatec (Convatec, Ickenham, UK) rod which does not require skin fixation. This rod is introduced under the loop of bowel using a Jaques' catheter with minimal trauma to the bowel[1]. The advantage of this technique is that it not only holds the bowel onto the surface of the skin satisfactorily, but also allows easy placement of the stoma bag adjacent to the bowel without the interference of a skin suture. In addition it is cheap, costing UK £1.70 per rod.

J. A. Grabham
A. Senapati

Department of Surgery
Queen Alexandra Hospital
Cosham
Portsmouth PO6 3LY
UK

1 Senapati A, Nicholls RJ. Formation of a loop stoma. *Br J Surg* 1991; 78: 23.

Infiltration of the gallbladder bed during laparoscopic cholecystectomy

Sir

A recognized method of facilitating bloodless dissection of the gallbladder from its liver bed during open cholecystectomy is to inject a solution of adrenaline between the gallbladder and its covering layer of peritoneum. We employ a similar technique during laparoscopic cholecystectomy

Once the cystic duct and artery have been safely divided, the gallbladder is placed on tension in preparation for dissection from the liver bed. A fine spinal needle is introduced through a puncture wound in the anterior abdominal wall under direct vision, and the tip is carefully inserted into the space between the gallbladder and its peritoneal covering. A 20-ml mixture of 0·5 per cent bupivacaine and 1 : 200 000 adrenaline is diluted with an equal volume of saline and injected, opening the space between the two structures. After a moment's pause, the gallbladder can then be dissected from the liver with scissors using minimal diathermy.

We find that this simple technique, by opening up the plane of dissection, allows quick and easy removal of the gallbladder from the liver bed. The amount of bleeding from the liver bed is reduced, and the infiltration may also contribute to the control of postoperative pain. The needle can also be used to aspirate bile from a distended gallbladder. We have experienced no complications from the technique, which we have used as part of our routine procedure in over 300 operations.

J. A. Grabham
P. C. Weaver

Department of Surgery
Queen Alexandra Hospital
Cosham
Portsmouth PO6 3LY
UK

Number of lymph node metastases is significantly associated with survival in patients with radically resected carcinoma of the ampulla of Vater

Sir

We read with interest the article by Dr Roder and colleagues (*Br J Surg* 1995; 82: 1693–6), who found that the number of involved lymph nodes affects survival after radical resection for ampullary cancer: patients with zero to two positive nodes had an actuarial 5-year survival rate of 41 per cent, while no patients with three or more positive nodes survived beyond 30 months. We recently reported that both no positive nodes and one to three positive nodes are favourable prognostic factors after such radical resection, with 5-year survival rates of 81 and 71 per cent respectively[1]. Both studies independently showed the effectiveness of radical surgery for patients with up to two or three positive nodes. Thus, we agree with the conclusion of Dr Roder and colleagues that 'radical resection and lymphadenectomy should be the treatment of choice for patients with tumours of the ampulla of Vater'. Unlike patients with breast cancer, those with ampullary cancer may benefit substantially from radical surgery However, it remains unclear whether more radical lymphadenectomy is effective for those with four or more positive nodes.

Dr Roder and colleagues did not discuss the impact of the location of positive nodes on survival. We have previously reported that patients with metastases confined to the pancreatoduodenal nodes have a significantly improved survival (5-year survival rate of 67 per cent) compared with those with metastases to the superior mesenteric nodes (5-year survival rate of 27 per cent)[1]. During the past decade, we have performed dissection of the superior mesenteric nodes to the right of the superior mesenteric artery for this disease, with the exception of 'early cancer', defined as cancer not penetrating the sphincter of Oddi[2]. In addition, we have dissected para-aortic nodes in patients with advanced disease clinically suspected of having positive regional nodes. As a result of this aggressive stance, three patients with positive superior mesenteric nodes have survived for 5 years[1]. Although the follow-up period in our series remains short, the value of radical lymphadenectomy should be clarified with the increase in long-term survivors with positive nodes.

Y. Shirai
T. Ohtani
K. Hatakeyama

Department of Surgery
Niigata University School of Medicine
1 Asahimachi-dori
Niigata City 951
Japan

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Authors' reply

Sir

We appreciate the comments of Drs Shirai, Ohtani and Hatakeyama confirming our observations on the effect of the number of involved lymph nodes on survival in patients after radical resection for ampullary carcinoma. We do not, however, agree with their comments regarding location of positive lymph nodes and survival. In our experience, now over 70 patients who have had a radical resection for carcinoma of the ampulla of Vater, we rarely observed positive lymph nodes at or along the superior mesenteric artery In contrast, more than 85 per cent of the positive nodes were located in the para-aortal region, i.e. lymph node station 13 of the Japanese Society for Biliary Surgery. On multivariate analysis only the number of positive lymph nodes, not the location of nodes, emerged as an independent prognostic factor. Further studies are, therefore, necessary before extensive lymphadenectomy along the superior mesenteric artery can be recommended as standard for patients with ampullary cancer and extensive lymph node metastases.

J. D. Roder
H. J. Stein
J. R. Siewert

Chirurgische Klinik und Poliklinik
Klinikum rechts der Isar der TU Munchen
Ismaningerstrasse 22
D-81 675 Munchen
Germany

Single-stage treatment for malignant left-sided colonic obstruction: a prospective randomized clinical trial comparing subtotal colectomy with segmental resection following intraoperative irrigation

Sir
I enjoyed the paper by the SCOTIA Study Group (*Br J Surg* 1995; 82: 1622–7). Since intraoperative colonic cleansing was introduced, left segmental colonic resection and primary colocolic anastomosis has become much less of a technical problem, but pathological conditions of the colonic wall, such as ischaemia, oedema, inflammation and ulceration, can still limit the performance of single-stage operations. Local mucosal changes may be accompanied by impaired healing of the primary anastomosis and the local mucosal condition of the colon should be evaluated at operation. The commonest finding is non-occlusive ischaemia[1] caused by raised intraluminal pressure in the obstructed colon or by circulatory shock. The first layer affected by hypoxia is the metabolically active mucosa. The initial histopathological change is subepithelial gaps. Next, the epithelium is sloughed and shed down to the base of the crypts[2]. Third, oedema develops and a membrane of necrotic epithelium covered by fibrin and infiltrated by inflammatory cells and bacteria appears. At this point the changes become macroscopically visible. Disintegration of the lamina propria is accompanied by severe oedema, ulceration and bleeding. If the muscularis and serosa are involved, gangrene and perforation may result.

Retrospective evaluation of 22 consecutive patients with left-sided colonic obstruction (personal data) has indicated that the primary anastomosis healed without problems in the absence of any macroscopic mucosal changes. However, in five patients anastomotic failure was associated with changes resembling those of radiation colitis, mucosal ulcers, inflammation involving the serosa and colonic perforation with severe peritonitis. The presence of macroscopically visible changes correlated well with the patient's circulatory condition (American Society of Anesthesiologists grade III and IV), the inflammatory parameters detected before operation, and with weight of colonic content over 3 kg (evacuated before the peroperative irrigation was started). Based on these retrospective findings, a single-stage procedure was performed in six subsequent patients in whom no macroscopic mucosal changes could be detected; all healed without leakage. As an alternative, a Hartmann's procedure was undertaken because of mucosal ulcers in one patient and tumour infiltration of the urinary bladder in another. Subtotal colectomy was performed due to mesocolic panniculitis in a third patient[3].

Macroscopic mucosal changes might, therefore, be the limiting factor for primary left-sided colonic anastomosis in patients with acute obstruction but this conclusion remains to be tested in a randomized study.

J. Danis

Hofmeister Strasse 70
A 2410 Hainburg an der Donau
Austria

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Aortic prosthetic infection: 50 patients treated by radical or local surgery

Sir
The article by Mr Hannon and colleagues (*Br J Surg* 1996; 83: 654), gave us important guidelines in the management of this difficult problem. During the past 5 years there has been considerable enthusiasm to try to prevent prosthetic graft infection by soaking the graft in rifampicin. Unfortunately, I have found that even this practice does not prevent graft infection. I recently had a patient who developed graft sepsis shortly after having a rifampicin-soaked graft inserted. The infecting organism was enterococcus, which was resistant to rifampicin.

J. G. Mosley

Department of Surgery
Leigh Infirmary
The Avenue
Leigh
Lancashire WN7 1HS
UK

Role of cytokines and growth factors in promoting the local recurrence of breast cancer

Sir
We read with interest the Review by Mr Reid and colleagues (*Br J Surg* 1996; 83: 313–20). The authors suggested that local recurrence in breast cancer could be attributed to growth factors and cytokines, derived from the surgical field environment, acting on free cancer cells (shed locally or systemically) and dormant residual cancer cells in the vicinity, thus causing local recurrence. They did not specify which factors and cytokines could mediate the process, but considered the local recurrence phenomenon in breast cancer to be different from that of other cancers bearing in mind that breast cancer is oestrogen-dependent

We would like to suggest that the higher aromatase activity and oestrogen concentration in the tumour-bearing quadrant of the breast (*versus* other breast quadrants) creates a pro-cancer environment favouring local recurrence near the surgical field. Growth factors and cytokines, particularly interleukin (IL) 6, play an important role in the regulation of oestrogen-synthesizing enzymes.

In addition, the macrophages and lymphocytes infiltrating the surgical field as part of the response to wound healing may secrete cytokines such as IL-6, which stimulate oestrogen synthesis in the area of the surgical field, thus raising local oestrogen concentration.

During the past few years, evidence has accumulated demonstrating that breast cancers produce growth factors and cytokines, which stimulate the enzymes involved in oestrogen synthesis (aromatase, oestradiol, dehydrogenase and oestrone sulphatase) to promote an oestrogenic environment favouring tumour growth[1]. Insulin-like growth factor (IGF) type I, IGF-II, IL-1β, IL-6 and tumour necrosis factor (TNF)[1] and TNF-α have been shown to stimulate the enzymes involved in oestrogen synthesis[2,3].

There is now a convincing body of evidence indicating that breast tumour location has an effect on aromatase activity in adjacent tissues[4,5]. The aromatase activity, and hence oestrogen synthesis, was found to be significantly higher in breast tumour-bearing quadrants than in other quadrants[4,5]. This finding was further supported by evidence of increased aromatase gene expression in breast tumour-bearing quadrants[6].

Miller and Mullen[7] have reported that IL-6 has an important stimulatory effect on aromatase activity in cultured tumour-derived fibroblasts Purohit *et al.*[5] showed that aromatase activity was increased in tumour-bearing quadrants, and this activity correlated with increased production of IL-6 by the tumour tissue. IL-6 may be produced by the cancer cells, the tumour fibroblasts and/or the macrophages and lymphocytes infiltrating around and within the tumour.

As it is known that macrophages and T lymphocytes (TH2) secrete IL-6, and that up to 50 per cent of the breast tumour volume may be composed of macrophages and lymphocytes, it is logical to assume that these cells secrete IL-6 (and other factors or cytokines) which stimulates oestrogen synthesis in the tumour-bearing quadrant. This hypothesis is supported by recent findings that the incidence of breast cancer was significantly reduced (by 25 per cent) among patients who had undergone transplantation receiving therapeutic immunosuppression[8], and that tamoxifen decreased the CD4 . CD8 ratio[9].

The lower local recurrence rate associated with quadrantectomy as compared with more conservative wide local excision[10] is consistent with our hypothesis. The macrophages and lymphocytes also infiltrate the surgical field as part of the healing response These cells may secrete cytokines, such as IL-6, which stimulate oestrogen synthesizing enzymes in the area, thus contributing to the creation of a pro-cancer environment encouraging local recurrence. However further research is required to confirm our suggestion and to provide a better understanding of the complex molecular events involving growth factors and cytokines in the local recurrence phenomenon of breast cancer

Future modulation of these factors and cytokines may provide a new means of improving local control

K. Mokbel

Academic Surgical Unit
St Mary's Hospital
London W2 1NY
UK

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Ileocaecostomy: an alternative surgical procedure for antegrade colonic enema

Sir

The article by Messrs March and Kiff (*Br J Surg* 1996; 83: 507–8) describes the novel approach of using the terminal ileum as a catheterizable conduit to allow antegrade colonic irrigation, with the ileocaecal valve as the mechanism preventing reflux of bowel contents and irrigant fluid.

While this is an interesting concept, we have some reservations. The ileocaecal 'valve' mechanism is incompletely understood, but available physiological evidence in man suggests that it does not act as a sphincter with persistent tonic contraction. Rather it exerts its sphincteric effect via variation in the rate of phasic contractions that occur over a considerable length of the terminal ileum, and are modulated by reflexes dependent on caecal and ileal integrity[1]. Caecal distension increases and ileal distension decreases the rate of these 'sphincteric' contractions. There are considerable periods of time when the ileocaecal 'valve' is relaxed, and reflux freely occurs from the caecum into the terminal ileum. The authors use only 5–7 cm of the distal ileum for their conduit This short segment combined with the separation from the remainder of the terminal ileum and its neurological influences is likely to disrupt the sphincteric mechanism of the ileocaecal junction and compromise its ability to act effectively as a continence mechanism

We were also surprised that the authors make no mention of an alternative operation, the continent colonic conduit, which we have previously described as another way of effecting antegrade colonic irrigation[2,3]. The colonic conduit has the theoretical advantage over the appendicostomy and the ileocaecostomy in that it can be constructed in the colon in a position most suited to deal with the underlying physiological abnormality. In cases of chronic constipation due to outlet obstruction, it can be formed in the descending or sigmoid colon. In cases of slow transit, it can be made in the ascending or transverse colon This manoeuvre obviates the need to irrigate the whole of the colon, which we believe to be unnecessary.

Some patients with appendicostomies have suffered abdominal pain and cramps that are thought to be due to the retrograde passage of irrigant fluid into the terminal ileum[4]. In addition, many find it necessary to administer phosphate enemas per conduit to achieve evacuation. There are reports of acute hyperphosphataemia and hypocalcaemia occurring with such enema usage[5–8]. Complications of this kind may be more likely in patients with an ileocaecostomy where there is no resistance to the passage of irrigant fluid through the ileocaecal anastomosis. We believe our conduit (which leaves the ileocaecal region intact) reduces the likelihood of caeco–ileal reflux.

The article does not give any detail of the size or appearance of the ileocaecostomy. The accompanying unscaled photograph suggests that the ileal mucosa is proud to the abdominal skin, which may reduce the cosmetic acceptability of the operation. The length of follow-up without stomal stenosis is not stated, but it is probable that a group of only seven patients does not represent a large enough sample to have the power to exclude such complications.

To prevent stenosis, we create a catheterizable conduit with a recessed orifice which is invariably less than 10 mm in diameter. This technique uses a V–Y flap of skin similar to that previously described[7]. All our patients have found the conduit cosmetically acceptable yet easy to intubate, and we have had only one episode of stomal stenosis in 20 patients at a median follow-up of 20 (range 7–37) months. Others have also found that some form of plastic skin flap construction reduces the incidence of stomal stenosis[5–8].

Although the authors only describe the use of their procedure in chronic idiopathic constipation, antegrade colonic irrigation has been successfully used for the treatment of faecal incontinence[2,4–7] Surgeons tempted to use the ileocaecostomy in the management of incontinence should be cautioned. If the procedure fails and surgical revision is required, the absence of the ileocaecal valve mechanism may exacerbate incontinence, resulting in a situation worse than before operation.

A. Maw
A. J. P. Eccersley
N. S. Williams

Academic Surgical Unit
St Bartholomew's and the Royal London School of Medicine and Dentistry
Royal London Hospital
Whitechapel
London E1 1BB
UK

1 Nasmyth DG, Williams NR. Pressure characteristics of the human ileocecal region – a key to its function. *Gastroenterology* 1985, 89: 345–51.
2 Hughes SF, Williams NS. Continent colonic conduit for the treatment of faecal incontinence associated with disordered evacuation. *Br J Surg* 1995; 82: 1318–20
3 Williams NS, Hughes SF, Stuchfield B. Continent colonic conduit for rectal evacuation in severe constipation. *Lancet* 1994; 343: 1321–4.
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9 Hunter MF, Ashton MR, Griffiths DM *et al.* Hyperphosphataemia after enemas in childhood: prevention and treatment. *Arch Dis Child* 1993; 68: 233–4.

Comparison of venous reflux in the affected and non-affected leg in patients with unilateral venous ulceration

Sir

Mr Bradbury and his colleagues have highlighted the importance of the popliteal vein segment in chronic venous ulceration (*Br J Surg* 1996; 83· 513–15) Using similar patient inclusion criteria (unilateral ulceration only, no previous ulceration in the contralateral leg, no evidence of arterial insufficiency, rheumatoid arthritis or diabetes mellitus), we have studied the colour flow duplex ultrasound results of 49 patients presenting to the community-based leg ulcer clinics in East Gloucestershire. The results are given in *Table 1*.

Table 1 Patterns of venous reflux in the ulcerated and non-ulcerated limbs of patients with unilateral ulceration.

	Ulcerated legs reflux	Non-ulcerated legs reflux	P*
CFV/SFV	9	2	—
Popliteal vein	18	9	0·07
LSV			—
Origin	35	29	—
Lower thigh	34	26	—
Below knee	27	11	0·02
SSV	10	8	—

CFV, common femoral vein; SFV, superficial femoral vein; LSV, long saphenous vein, SSV, short saphenous vein. *Corrected χ^2 test

It is confirmed from these early results of our ongoing prospective study that reflux in the superficial venous system below the knee, including the calf perforators, is also significantly greater in ulcerated than non-ulcerated limbs. The role of operation in chronic venous ulceration, including subfascial endoscopic perforator ligation, remains unclear, and further investigation is indicated.

A. S. K. Ghauri
A. J. Grabs
I. Nyamekye
K. R. Poskitt

Department of Vascular Surgery
Cheltenham General Hospital
East Gloucestershire
NHS Trust
Sandford Road
Cheltenham GL53 7AN
UK

Authors' reply

Sir

We thank Messrs Ghauri, Grabs, Nyamekye and Poskitt for their interest in our recent article, and are interested to note that they too found an increased prevalence of popliteal vein incompetence in the affected legs of patients with unilateral leg ulceration of apparently 'pure' venous aetiology However, in addition to excluding patients in whom non-venous aetiological factors had been identified, we also excluded patients who had undergone previous venous surgery. We felt that this was extremely important if we were to achieve a true comparison of reflux between ulcerated and non-ulcerated legs that had not been previously 'tampered' with surgically. The surgical history of the patients in Mr Poskitt's series was not stated in his letter, but previous varicose vein surgery in some of his patients might possibly account for differences between his series and ours, with respect to the prevalence of superficial venous incompetence. Thus, Mr Poskitt and his colleagues may have found a lower incidence of superficial venous incompetence in the non-ulcerated legs because their patients had previously undergone saphenous and/or perforator ligation on that side. With respect to perforators and their ligation, we agree that this is an area that is in urgent need of further scientific investigation, particularly with the increasing popularity of subfascial endoscopic perforator surgery.

A. Bradbury
C. V. Ruckley

Vascular Surgery Unit
Academic Surgical Unit
10th Floor
Queen Elizabeth the Queen Mother Building
St Mary's Hospital
London W2 1NY
UK

Correlation between Acute Physiology and Chronic Health Evaluation (APACHE) III score and immunological parameters in critically ill patients with sepsis

Sir

We read with interest the paper by Dr Rogy and colleagues (*Br J Surg* 1996; 83: 396–400) describing physiological and immunological parameters in ten critically ill patients. We performed daily Acute Physiology and Chronic Health Evaluation (APACHE) III scoring and C-reactive protein (CRP) measurement on five consecutive patients with severe acute pancreatitis admitted to intensive care in the second half of 1995. APACHE III scores and CRP measurements at admission and 72 h are shown in *Fig 1* together with patient demographics and outcome.

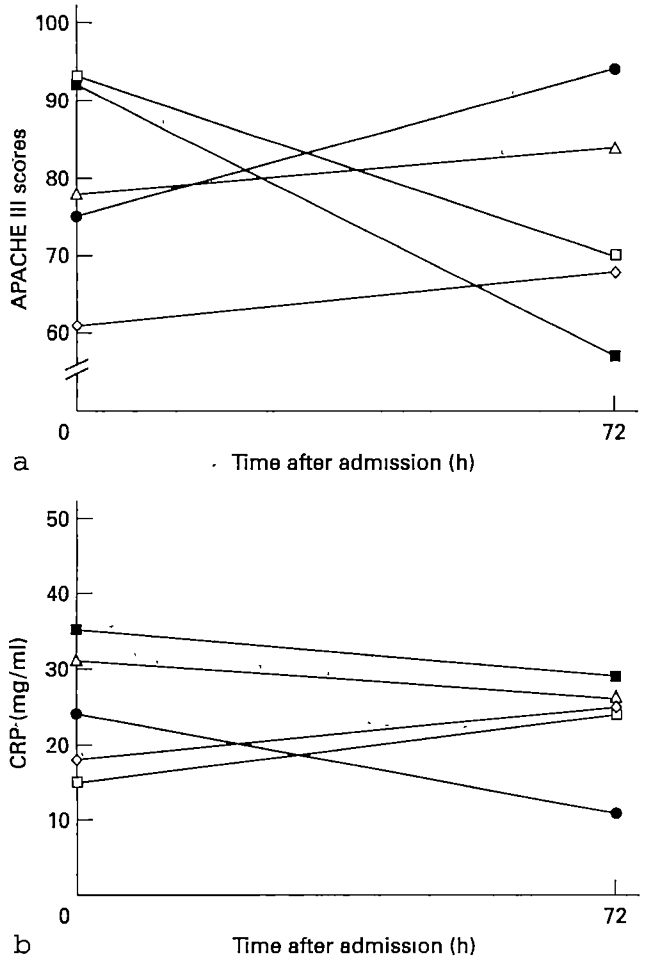

Fig. 1 Changes in APACHE III score and CRP in five patients with severe acute pancreatitis between intensive care admission and 72 h. ◇, 65-year-old man who left intensive treatment unit (ITU) on day 90; □, 39-year-old woman who left ITU on day 57 but later died; ■, 65-year-old man who died on day 14; ●, 65-year-old man who died on day 23; △, 80-year-old woman who left ITU on day 25

We found no correlation related to outcome in this small group with pancreatitis. Any correlation in a larger sample would be unhelpful for prediction of outcome because of individual variation.

We cannot support the findings of Rogy *et al.* that APACHE III scoring at 72 h predicts the outcome of critically ill patients when applied to severe acute pancreatitis.

M. D. Barber
I. R. Armstrong

Departments of Surgery and Anaesthetics
Royal Infirmary of Edinburgh
1 Lauriston Place
Edinburgh EH3 9YW
UK

Author's reply

Sir

We find no reason to quibble with the observations of Messrs Barber and Armstrong. Indeed, there is currently no statistical basis on which to assume that any physiological scoring system will track the course of patients with evolving inflammatory disease. However, our observations were derived from patients with infection. It is neither intuitively nor statistically unlikely that such patients might exhibit an acute reduction in physiological scoring in response to specific antimicrobial and resuscitative efforts[1]. Rather, we were impressed to find that immunocyte function was acutely responsive in this setting.

S. F. Lowry

Cornell Medical Center
525 East 68th Street
New York
New York 10 021
USA

1 Knaus WA, Harrell FE, Fisher CJ Jr *et al.* The clinical evaluation of new drugs for sepsis: a prospective study design based upon survival analysis. *JAMA* 1993; 270: 1233–41.

British Journal of Surgery 1996, 83, 1307–1309

Book reviews

Electrosurgery in Operative Endoscopy

A. Wattiez, S. Khandwala and M.-A. Bruhat. 250 × 175 mm. Pp. 274. Illustrated. 1995. Oxford: Blackwell Science. £49.50.

The authors rightly state that knowledge of electrical principles among most surgeons is very limited; the aim of this book is to correct this deficit. Written in a not overly-technical style, the authors have tried to keep the theoretical aspects to a minimum while concentrating on practical aspects of electrosurgery. By and large they have succeeded. The first half deals with the fundamentals of electrical energy, electrosurgical waveforms and the creation of different tissue effects, and monopolar and bipolar electrosurgery. While amply illustrated with line drawing and diagrams, the circuit diagrams at the beginning of the book may be off-putting to those without a background in physics. There are individual chapters on electrosurgery in laparoscopy, laparoscopic sterilization, endoscopic excisional surgery and underwater surgery (i.e. urological and gynaecological surgery). The slight bias towards gynaecological surgery probably reflects the background of the authors. Contributions from other endoscopic surgeons might have given a broader overview. The aetiology and prevention of accidental electrosurgical burns is the most important topic in this book and is well covered. There are also chapters on the effects of electrosurgery-induced electromagnetic interference on electrocardiograms, pacemakers and videoimaging equipment. Comprehensive references are given as well as a list of recommended practices. A chapter defining the role of theatre nurses in electrosurgical safety is also included. Although aimed specifically at the endoscopic surgeon, much of the contents is of relevance to other surgical specialties. The best way to prevent injuries is to understand them, and in this respect, the authors have succeeded in their aim.

A. Darzi

St Mary's Hospital
Praed Street
London W2 1NY
UK

Laparoscopic Colorectal Surgery

J. W. Milsom and B. Böhm. 260 × 180 mm. Pp. 256. Illustrated. 1996. New York: Springer. DM168.

This book is well written, very readable and extremely topical. The subject is introduced with a comprehensive history of laparoscopic surgery and then follow seven chapters concerning equipment, instruments, tissue dissection and techniques both for basic laparoscopic surgery and for the advanced and specialized field of coloproctology. Precise details are given of intra-abdominal suturing techniques, port insertion, cannula site closure, indications and postoperative management Curiously, the chapter on major operative procedures in laparoscopic colorectal surgery begins with ileal resection. The rest of this chapter describes the laparoscopic techniques of ileocolectomy, right hemicolectomy, proctosigmoidectomy, abdominoperineal resection and total abdominal colectomy. The last procedure is concluded by a double-stapled ileorectal anastomosis with no reference to, or description of, an ileal pouch. The subsequent two chapters are concerned with the fashioning and closure of stomas, suture rectopexy for prolapse and adhesiolysis. The final chapters concern advantages and disadvantages of laparoscopic colorectal surgery, and the education of the surgical team in the technique and practice of the new operations.

For the surgeon embarking upon laparoscopic colorectal surgery this book is essential reading; particularly pertinent are the excellent sections on the training and skills necessary. Unfortunately, the actual operative descriptions are not as comprehensive as might be expected. Of the operative diagrams of the positioning of the theatre team and the port sites, too much space has been incorporated and most are full-page and repetitious. There are only line diagrams of the techniques, which are technically clear and good, but could be improved on if associated with colour photographs which are strikingly absent. Some techniques are missing, notably the mesh rectopexy, retroperitoneoscopy and colectomy without pneumoperitoneum. Stoma construction is well described and the diagrams throughout are clear and of the highest standard.

Although claimed to be the first surgical text on the subject, it compares unfavourably with the book, published a year ago and with the same title, edited by Monson and Darzi, which is superbly illustrated with colour photographs of operative techniques.

F. P. McGinn

Southampton General Hospital
Tremona Road
Southampton SO9 4PE
UK

Shackelford's Surgery of the Alimentary Tract. 4th ed. (5 volumes)

G. D. Zuidema, M. B. Orringer, W. P. Ritchie Jr, J. G. Turcotte, R. E. Condon and L. M. Nyhus (eds). 285 × 220 mm. Pp. 556 (Vol. 1), 423 (Vol. 2), 670 (Vol. 3), 474 (Vol. 4), 652 (Vol. 5). Illustrated. 1996. Philadelphia, Pennsylvania: W. B. Saunders. £330.

This five-volume set presents a fairly detailed and up-to-date treatise on gastrointestinal surgery. Although it is the fourth edition, surprisingly it is relatively unknown on the European side of the Atlantic. It has grown from a single-editor edition in 1955 through a multieditor to a multiauthor fourth edition now.

It is, on the whole, well written and the depth of coverage in general includes considerable operative detail. Despite a largely American authorship, references and text have an international flavour and the British reader will find much that is familiar and little to quarrel with. It claims to provide an authoritative and up-to-date text which is valuable because of 'dramatic changes in surgical practice during the past few years'. It achieves this objective in part but it is disappointing to find some chapters rather superficial. The one on intestinal intubation is somewhat dated and others, such as those on basic sciences and operative surgery in volume 4, 'Colon and Rectum', somewhat limited in scope. On the other hand, several chapters are outstanding. They include those on anatomy and physiological diagnostic studies and the complications of oesophageal surgery in volume 1. The chapter on anatomy in volume 2 is excessively detailed in comparison with that in volume 4 where the text is somewhat limited by the space available. The general appearance of the book would have benefited from some colour illustrations, especially for anatomical specimens and histology.

The set suffers from the common problem of variability of quality, which is seen in all multiauthor books. There are 50 or more authors writing in each volume and their variability of style is reflected by the chapter reference lists which vary from a limited and rather dated six to in excess of 350. Unfortunately the long lists of references provide a comprehensive rather than a critical review of the literature and indicate only the accessibility of the author to computerized Medline.

This work is in competition with several other excellent state-of-the-art surgical texts and so will probably remain popular only in the USA. At UK £330 for the five-volume set, it will grace the shelves of only the most affluent surgical libraries in the UK; there the surgical trainee may find much of interest while the specialist may find it reassuring rather than informative.

B. R. Davidson
A. A. M. Lewis
A. Watson
K. E. F. Hobbs

Royal Free Hospital
Pond Street
London NW3 2QG
UK

Textbook of Surgery

Roshan Lall Gupta. 273 × 215 mm. Pp. 677. Illustrated. 1996. New Delhi: Jaypee Brothers Medical Publishers. Price not provided.

This is an all encompassing textbook of surgery from the Indian subcontinent The self description says that it 'aims to serve the academic needs of all undergraduate medical students, residents and young practising clinicians in a comprehensive manner'.It certainly does appear to cover just about all aspects of surgical practice to a greater or lesser degree. The style is relatively old fashioned and in some respects this is reflected by some content, which shows a scope of pathology which is rarely seen in the Western world. The aim of the book would appear to be to produce such a volume as cheaply as possible and in some respects that is no bad thing. However, this aspect is relatively obvious. I believe that a comprehensive surgical textbook is possibly better done elsewhere, although I suspect at a greater cost. In conclusion, I suspect this is probably the incredibly cheap comprehensive generalist's surgical textbook. I imagine, in certain areas of the world, it will be popular among its target audience, but I do not think there is a particular market for this in the UK.

P. A. Stonebridge

Ninewells Hospital
Dundee DD2 1UB
UK

Recent Advances in Surgery 5

Roshan Lall Gupta (ed). 226 × 149 mm Pp. 349. Illustrated. 1996. New Delhi: Jaypee Brothers Medical Publishers. Price not provided.

This booklet is soft-cover, lightweight and cheaply printed in India (a few words are hardly legible). Thirty-five authors (all Indian except one Japanese), from India (28), USA (3), Abu Dhabi (2), Australia and Japan (one each) contributed 21 'topics of deep interest to the postgraduate students and practising surgeons, especially such issues that are related to the clinicians in the Indian sub-continent'. The cover claims that 'this volume examines the development of multiple areas of general surgery ranging from penile revascularization, anorectal anomalies, disorders of the pancreas, problems of the GI tract ... to the management of cancer of the head and neck'

The first contribution is presented as 'a detailed chapter by the Editor reviewing recent progress in surgery encapsulates the current trends'. I found this chapter shallow in places and biased. Sixty-four of the quoted 212 references (11 from India) were published before the 1990s (a few in the 1960s) and so cannot be considered recent. Recent topical advances in molecular biology, sepsis, hepatic surgery and trauma were not mentioned, while a 'biologically engineered trachea' was discussed. Only six of the 21 chapters included material of special interest to the Indian subcontinent, such as: 'Head and neck cancers', 'Reconstructive surgery in leprosy', "'Home made' device for percutaneous gastrostomy", 'Tropical pancreatitis' (an excellent chapter), and 'Inflammatory bowel disease in India'. In the chapter entitled 'Laparoscopic surgery: its relevance to Indian urology', I could not find the 'Indian relevance', while in chapters such as 'Use of lasers in surgery' I did not find relevance even for our residents here in New York. A few chapters like 'Unusual and difficult surgical encounters on benign biliary disease' are enjoyable and very good reading The quality of reference lists varies among contributions and many key references are omitted. Not knowing much about Indian surgery I consulted our resident Dr Ramesh Paladugu who informed me of the huge market for surgical literature in the Indian subcontinent, represented by many thousands of residents and surgeons administrating Western surgery under adverse circumstances to a population of over 700 million. Dr Paladugu tells me that the 'Recent Advances in Surgery' series is very popular among residents in India, at a price of 300 rupees (about US $10) it is much more affordable than foreign books. Sections of this book represent valuable reading for residents and an update for practising surgeons At this price I would consider it a bargain.

M. Schein

Methodist Hospital
506 Sixth Street
Brooklyn
New York 11215-9008
USA

Principles of Surgical Research. 2nd ed.

R. T. Mathie and K. M. Taylor (eds). 240 × 168 mm. Pp. 269. Illustrated. 1995. Oxford: Butterworth-Heinemann. £40.

This is an excellent small book containing a wealth of information, principally directed at a junior doctor beginning research. The book attempts to be comprehensive and is set up in four sections. Section 1, designing and starting a research project; Section 2, conducting a research project; Section 3, computing and statistics, and Section 4, how to do it. The first section has some meaty philosophical commentaries; although, as Kenneth Calman states in the foreword, the reason for doing research is often a material one in climbing the ladder, the philosophy that all good surgeons should do research seems reasonable. There are excellent chapters on information management and applying for a research grant. The section on conducting a research project contains much needed information and includes statistics, the use of animals and the ethics of research. A short introduction to molecular biology in surgical research may seem slightly inappropriate in the book, but it is well written The third section contains useful information on computing and statistics. The final section contains guidance on the presentations of papers, writing a paper, illustrating presentations and writing and submitting a thesis. Again this is highly useful information.

This reviewer would classify the volume as essential reading for any young clinician starting out on research It contains information which can be used at timely intervals during such work. Although directed at surgical researchers the book would be equally useful to those embarking on other areas of medical enquiry. Many of the technologies and, indeed, areas of research are now shared by interdisciplinary teams. Perhaps one thing that should be added in terms of advice is that when starting a project the young researcher should seek to become attached to a critical mass group with an excellent record in clinical research. This usually ensures success; going it alone can be difficult.

K. D. Buchanan

Queen's University of Belfast
University Road
Belfast BT7 1NN
UK

Churchill's Pocketbook of Surgery

A. T. Raftery. 187 × 105 mm. Pp. 485. Illustrated. 1996. Edinburgh: Churchill Livingstone. £13.50.

'What is the good of my writing a thundering big book, when everything is in this little green book so despicable for its size?'. Thus commented Charles Darwin to Thomas Henry Huxley on seeing a fourpenny pamphlet in which the essential arguments of *The Origin of Species* were summarized. *Churchill's Pocketbook of Surgery* is white, not green, but one can imagine a modern surgical Darwin repeating his famous namesake's comment. The truth is that the modern medical student prefers to buy small didactic books, not, as AT Raftery suggests, because of any impecunity, but because students like short succinct 'learning bites' as a way of coping with an ever expanding curriculum. This book admirably provides the undergraduate surgical bite.

Several pocketbooks are now available but this one must rank in the forefront of the genre. The book is sturdily made, produced in three colours and fits snugly into the pocket. It is easy to find one's way around this book with a contents list on the front cover and a good index at the back. The entire spectrum of surgery is covered and important data are highlighted in boxes and tables. The text is snappy but there are some wonderful typographical errors (e.g. carcinoma of the female disease (*sic*), reccurent (*sic*), iverticulitis (*sic*)). The medical students who have seen the book liked the tables of normal biochemical and haematological values given on the inside of the back cover but regretted the dearth of illustrations. Like most surgical books, this one is predominantly based on pathology, but an attempt is made at a symptom-based approach in some areas (e.g. acute abdomen). House surgeons and SHOs will not find this book particularly useful but medical students will devour it.

P. A. Grace

Limerick Regional Hospital
Dooradoyle
Limerick
Ireland

Human Anatomy. Color Atlas and Text. 3rd ed.

J. A. Gosling, P. F. Harris, J. R. Humpherson, I. Whitmore and P. L. T. Willan. 275 × 215 mm. Pp. 360. Illustrated. 1996. London: Mosby-Wolfe. £24.95.

This anatomy textbook comprises a systematic series of excellent photographs of cadaveric dissections which are accompanied by elegant explanatory diagrams. The text is succinct and exactly matches the relevant illustrations. In this edition each chapter has been supplemented with a section of multiple choice questions and a set of short clinical case histories chosen to illustrate pertinent anatomical points The nature of the book precludes consideration of some important anatomical principles, such as the segmental anatomy of the lungs and liver, and anatomical variation cannot be demonstrated when the illustrations are based on single dissections However, the authors, illustrators and photographers have been extremely successful in achieving their objective. As a manual for undergraduates or basic surgical trainees requiring practical instruction in gross anatomy, this book has much to commend it. It is a beautiful piece of work.

Z. H. Krukowski

Aberdeen Royal Infirmary
Foresterhill
Aberdeen AB9 2ZB
UK

British Journal of Surgery 1996, 83, 1310

Notices and announcements

3–4 September 1996
Anal Continence Conference
Eastbourne, UK
Information: Mr B. J. Stoodley, Department of General Surgery, Eastbourne District General Hospital, Kings Drive, Eastbourne BN21 2UD, UK

3–7 September 1996
5th World Congress of OESO
Paris, France
Information: Professor R. Giuli, Scientific Director, OESO, 2 Boulevard du Montparnasse, 75015 Paris, France

9–27 September 1996
Hammersmith FRCS Course
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

16–20 September 1996
An Update in Surgery for General Practitioners
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

18–19 September 1996
Fundamental Techniques of Plastic Surgery
Swansea, UK
Information: British Association of Plastic Surgeons, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

18–20 September 1996
Society for Minimally Invasive Therapy 8th International Meeting
Milan, Italy
Information. G. Carminati, Istituto di Urologia, Universita degli Studi, Via della Commenda 15, 20122 Milan, Italy

19–21 September 1996
International Meeting on Inflammatory Bowel Disease
Capri, Italy
Information: Professor R. Caprilli, Cattedra di Gastroenterologia, Università de L'Aquila, Via S. Sisto 22E, 67100 L'Aquila, Italy

27–28 September 1996
Advanced Minimal Access Surgery for Theatre Personnel
Liverpool, UK
Information: J. O'Leary, Training Manager, MASTER Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

27–28 September 1996
2nd Joint Meeting of Hungarian–Italian Pancreatic Surgeons
Verona, Italy
Information C. Bassi, Dipartimento di Scienze Chirurgiche, Policlinico Universitario di Borgo Roma, Università di Verona, 37134 Verona, Italy

3–4 and 9 October 1996
Laparoscopic Rectopexy
Liverpool, UK
Information: J. O'Leary, Training Manager, MASTER Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

6–11 October 1996
Clinical Congress of the American College of Surgeons
San Francisco, California, USA
Information. Nancy Sutton, Convention and Meetings Division, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-9424, USA

11 October 1996
Vascular Surgery – is it worthwhile?
Newcastle, UK
Information. Mr J. Chamberlain, Freeman Hospital, Freeman Road, High Heaton, Newcastle-upon-Tyne NE7 7DN, UK

13–19 October 1996
Recent Advances in Surgery of the Liver, Pancreas and Biliary System
Edinburgh, UK
Information: International Seminars Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

16–18 October 1996
1st International Congress of the European Club for Pediatric Burns – Current Concepts in Pediatric Burn Care
Zurich, Switzerland
Information: M Meuli, Director Pediatric Burn Center, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland

16–18 October 1996
Lasers in Arthroscopic Surgery
London, UK
Information. Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

19–24 October 1996
1st World Congress of Surgical Endoscopy
Beijing, China
Information: J. M. Phillips, General Chairman, 1st World Congress of Surgical Endoscopy, 13021 East Florence Avenue, Santa Fe Springs, California 90670-8774, USA

21–22 October 1996
'State of the Art' Surgery for Breast Specialists
Manchester, UK
Information. Miss J. Smith, Department of Surgery, University of South Manchester, Nell Lane, West Didsbury, Manchester M20 8LR, UK

21–23 October 1996
4th Postgraduate Course in Surgery
Bangkok, Thailand
Information. V Sachakul, Secretary General, Local Organizing Committee, Department of Surgery, Pramongkutklao Hospital, 315 Rajvithi Road, Bangkok 10400, Thailand

23–25 October 1996
Spinal Surgery Course
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

24–26 October 1996
4th European Conference on General Thoracic Surgery
Cordoba, Spain
Information: Dr F. J. L Pujol, C/.Caño, 3-1.°, 1, 14001 Cordoba, Spain

27–30 October 1996
8th Overseas Meeting of the Royal College of Surgeons of Edinburgh jointly with the College of Surgeons of Hong Kong
Hong Kong
Information. The Clerk to the College, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

13–16 November 1996
3rd Hong Kong International Cancer Congress and the 7th Epstein–Barr Virus and Associated Diseases Congress
Hong Kong
Information: HKICC Secretariat, 2/F., Professorial Block, Queen Mary Hospital, Hong Kong

14–17 November 1996
3rd Congress of the International Association of Gerontology. European Region – Clinical Section
Thessaloniki, Greece
Information: Athos City Congress, 5 Agias Sofias Street, Thessaloniki 54623, Greece

19–22 November 1996
European Course on Laparoscopic Surgery
Brussels, Belgium
Information. Administrative Secretariat, Conference Services, Avenue de l'Observatoire, 3 bte 17, B-1180 Bruxelles, Belgium

Instructions to authors

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For detailed guidance on the handling of statistical material, authors should consult *Br J Surg* 1991; 78: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of data, the *analysis* of data and the *interpretation* of results.

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There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the P value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual P values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant'. Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values.

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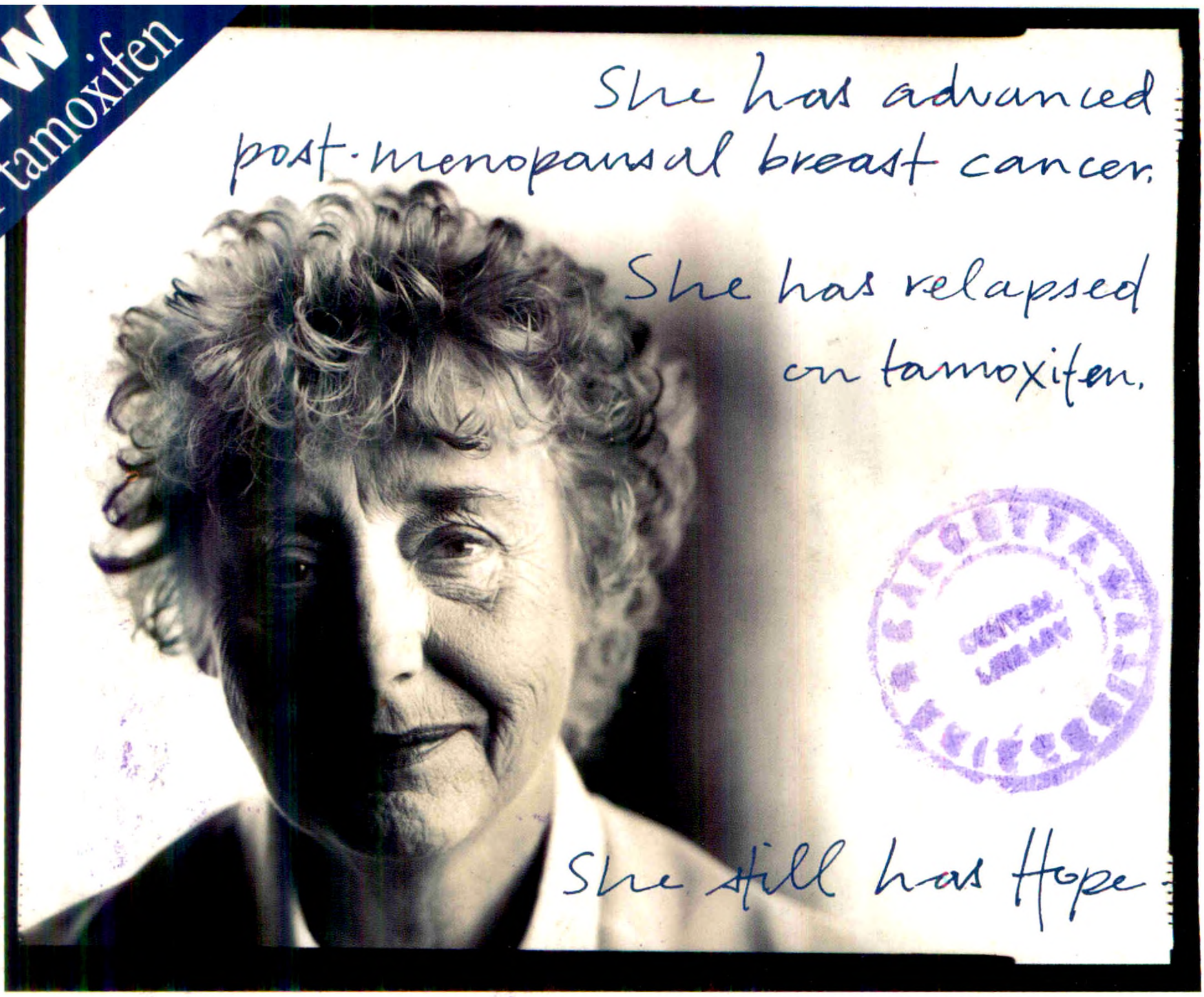

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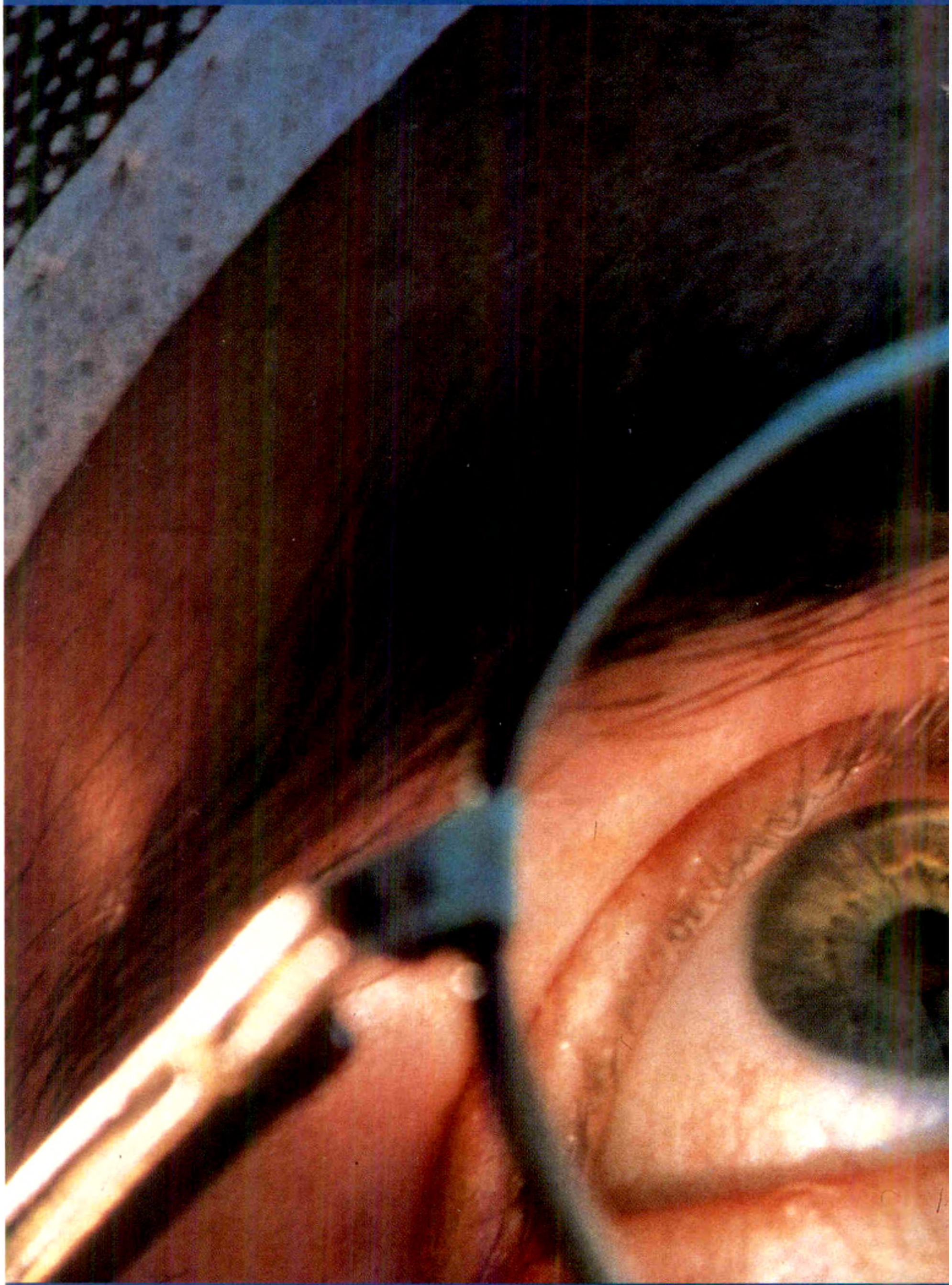

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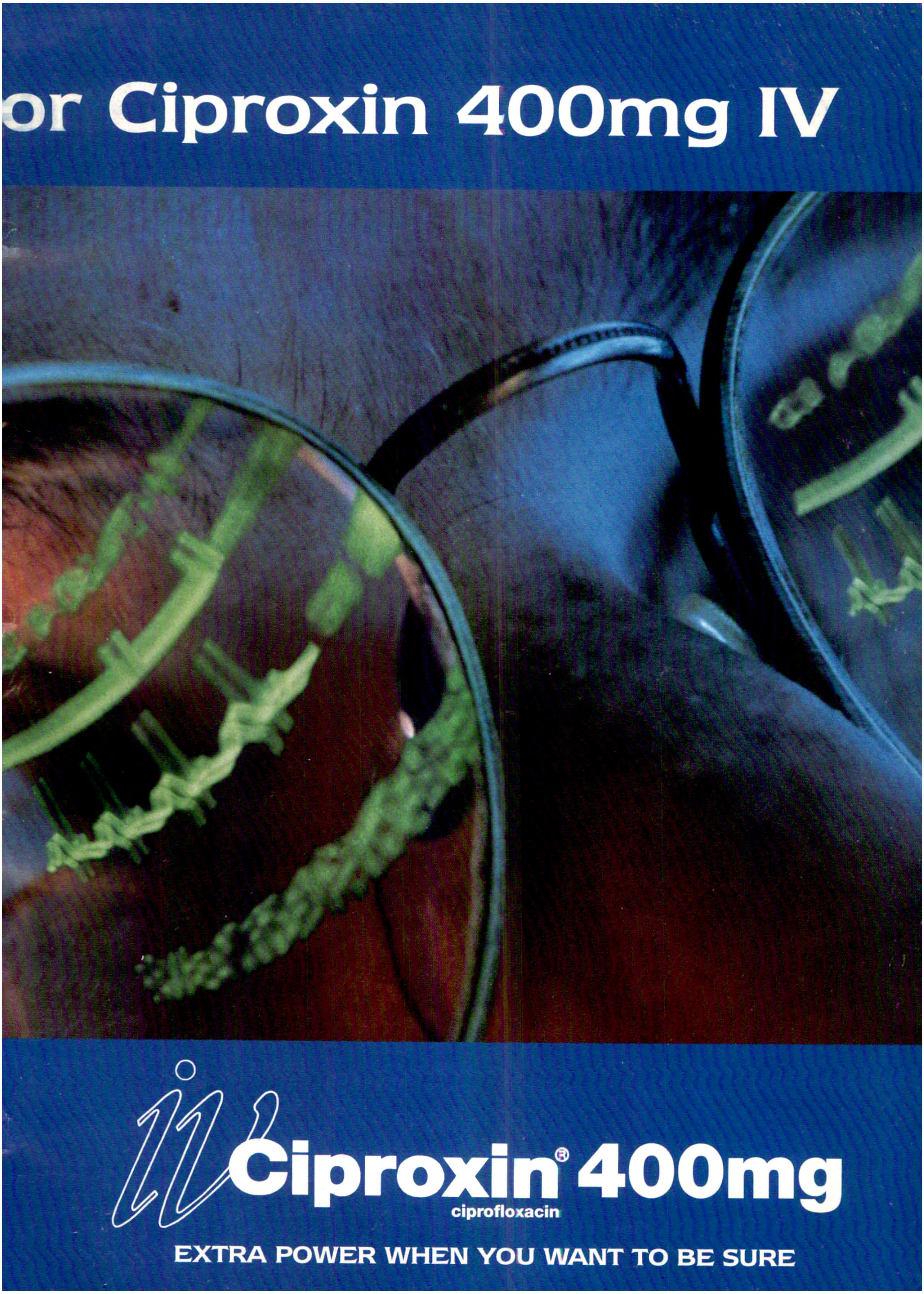
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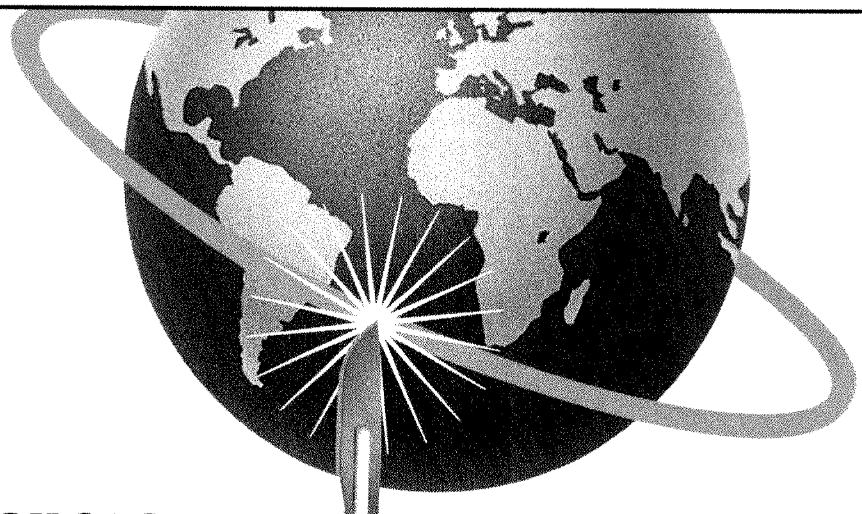

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THE AUSTRALIAN AND NEW ZEALAND JOURNAL OF SURGERY

Chairman &
Editor in Chief
G. J. A. Clunie

ISSN 0004-8682
Published monthly

Editors
J. Ludbrook
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The Australian and New Zealand Journal of Surgery is published monthly. The subscription rates for 1995 (Volume 65) Aus$276.00 (Australasia), US$392.00 and Aus$560.00 (elsewhere). The Journal is dispatched to subscribers outside Australasia by surface air-lifted post.

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British Journal of Surgery 1996, **83**, 1313–1315

Leading articles

Surgical management of gastro-oesophageal reflux disease

The past decade has seen important developments in the management of gastro-oesophageal reflux disease (GORD). The emergence of powerful antisecretory drugs has increased the proportion of patients whose oesophagitis can be healed to around 90 per cent, which some predicted would sound a death knell for antireflux surgery. However, there have been equally exciting surgical developments, arising from greater understanding of the mode of action of antireflux procedures and the genesis of mechanical complications, and, more recently, the adaptation of several antireflux procedures to a laparoscopic approach.

Although GORD is a common disorder affecting up to 40 per cent of the population, the majority have mild disease, resulting from transient relaxation of a normal lower oesophageal sphincter (LOS); this can be controlled effectively with lifestyle changes and appropriate pharmacological treatment. A minority have more severe disease, with ulcerative, circumferential oesophagitis, often associated with severe impairment of the LOS and peristaltic function, and a tendency to develop complications such as ulcer, stricture and Barrett's columnar-lined oesophagus (CLO); 44 per cent of these patients will have unhealed oesophagitis after 2 months of treatment with omeprazole 40 mg daily[1]. GORD is a lifelong condition and, of those who can be healed, over 80 per cent relapse when treatment is stopped; even if omeprazole is continued in therapeutic dosage, up to 30 per cent relapse by 1 year. The desirability of lifelong virtual anacidity, particularly in young patients, is questionable, even though serious consequences of hypergastrinaemia and altered bacterial colonization are theoretical or confined to animal studies. A recent randomized controlled trial showed antireflux surgery to be superior to long-term therapy with H_2-receptor antagonists[2].

Failure of medical treatment is the principal indication for antireflux surgery and may encompass incomplete control of symptoms, persistent oesophagitis or frequent relapses. Reduced likelihood of success may be signalled clinically if regurgitation is a predominant feature, particularly if associated with laryngeal or respiratory symptoms, endoscopically if circumferential erosive oesophagitis is present and functionally if there is evidence of LOS failure or a significant alkaline component to the refluxate. Antireflux surgery should be discussed with young, fit patients who can only be maintained in remission on long-term antisecretory drugs; increasingly, patient preference is an indication for surgery. Complications of GORD, such as ulcer, stricture and Barrett's CLO, while associated with the most severe pathophysiological disturbances, are not absolute indications for operation, although many would favour surgery in younger patients. Controlled studies of Barrett's CLO have shown that antireflux surgery promotes greater healing of stricture than acid suppression, arrests progression of columnarization in a higher proportion of patients and promotes regression in a minority[3]. However, there is no current evidence to demonstrate that antireflux surgery can prevent adenocarcinoma.

Of the available operations, the 'floppy' Nissen fundoplication is the most popular, resulting in symptomatic and objective control of reflux in 91 and 83 per cent of patients respectively[4]. There have been several modifications of the original technique, designed to reduce the incidence of mechanical complications, principally slippage, disruption, dysphagia, gas bloat and inability to belch or vomit. These have included performing a short wrap 1–2 cm in length over a 50–60-Fr bougie, the addition of a crural sling repair and division of the short gastric vessels. These modifications have reduced the incidence of troublesome dysphagia to 3 per cent, but the incidence of gas bloat remains at 11 per cent and that of inability to belch or vomit is considerably higher[4]. These problems are believed to relate to the creation of a supracompetent LOS which relaxes imperfectly[5].

Concern about these issues has resulted in a revival of interest in partial fundoplication procedures, which were previously believed to offer inferior reflux control. The 'physiological' antireflux procedure described by Watson and colleagues[6] is predicated on the hypothesis that correction and accentuation of the factors known to contribute to the valvuloplasty component of competence (the crural sling, angle of His and length of intra-abdominal oesophagus) may enable reflux control without total fundoplication and, by maintaining LOS relaxation, may reduce the incidence of mechanical complications. The hypothesis has been confirmed with subjective and objective reflux control equalling the best reported results of Nissen fundoplication, but with virtual abolition of mechanical complications, findings which have been confirmed by others. The Lind and the Toupet partial fundoplication procedures have been compared in three randomized controlled trials with a 'floppy' Nissen fundoplication, with equivalent subjective and objective reflux control being demonstrated. However, mechanical complications were more troublesome with the Nissen procedure, persisting at late assessment up to 5 years in two studies[7,8]. There has recently been an increased deployment of partial fundoplication procedures, particularly among advocates of the 'tailored' approach to antireflux surgery; patients with manometrically normal oesophageal body motility undergo a 'floppy' Nissen procedure and those with significant peristaltic impairment, felt to be at greatest risk of developing complications with a total wrap, undergo a partial fundoplication[9]. That such an approach has not compromised the degree of reflux control is further support for the efficacy of currently used partial fundoplication procedures, as patients with significant peristaltic impairment are known to be the most severe refluxers[10].

Undoubtedly, the most exciting development in antireflux surgery has been the introduction of laparoscopic fundoplication and the demonstration that, at least in the short term, similar subjective and objective results to the open approach can be achieved with most of the commonly used procedures, but with more rapid recovery. However, there is some evidence that the incidence of mechanical complications and impaired LOS relaxation may be higher after laparoscopic Nissen fundoplication than with the open approach[11]. Some 6000 cases of various types of laparoscopic fundoplication have now been reported worldwide, with an overall success rate of 90 per cent, a mortality rate less than 0·5 per cent but with a morbidity rate between 5 and 10 per cent. Rather disturbingly, oesophageal and gastric injury has featured prominently in reported morbidity and mortality, emphasizing the necessary prerequisites of experience in oesophageal surgery and supervised training in laparoscopic fundoplication. The majority of patients are suitable for a laparoscopic approach, although difficulty may be encountered in the very obese and in those with transmural oesophageal inflammation. Providing the early results of laparoscopic fundoplication are continued into the long term, it will offer an attractive and cost-effective alternative to lifelong medication, particularly for young patients. However, any relative advantage must be assessed by randomized controlled trials encompassing cost and quality of life measurement in addition to the more traditional endpoints.

In 1996, effective, long-term reflux control can be achieved by antireflux surgery in expert hands and this is more likely to be operator than procedure dependent. There is a strong case for concentrating antireflux surgery in centres where expertise is strong, and where there is a sufficient throughput of patients and facilities for oesophageal measurement, relevant both to preoperative assessment and quality control of results. The remaining area with potential for further improvement is the elimination, as far as possible, of the small but definite incidence of troublesome mechanical complications which is probably more procedure than operator dependent. If we are to gain the support of our gastroenterological colleagues in mounting randomized controlled trials of optimal medical therapy *versus* laparoscopic fundoplication, we should be prepared to establish, by similar means, which procedure provides the best combination of effective reflux control, avoidance of mechanical complications and improved overall quality of life.

A. Watson

Department of Surgery
Royal Free Hospital School of Medicine
London NW3 2QG
UK

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British Journal of Surgery 1996, **83**, 1316–1318

Magnetic resonance mammography

Recent technical advance in magnetic resonance imaging (MRI) has facilitated the development of magnetic resonance mammography (MRM) as a new breast imaging modality that offers significant potential advantages over conventional radiographic mammography. While the role of conventional mammography has long been established for both screening and assessment of palpable lesions, there are certain groups of patients for whom this technique has inherent disadvantages. Previous surgery to the breast causes parenchymal scarring, which may prevent detection of malignant lesions, and mammographically dense breasts, found particularly in younger women, may obscure an underlying malignancy. In these younger patients susceptibility to radiation-induced breast cancer is also a definite concern. For these groups in particular MRM offers a potentially significant clinical advantage.

Some of the earliest studies of the diagnostic applications of MRI were performed on patients with breast cancer[1]. However, the results proved disappointing, with MRI faring no better than conventional mammography in delineating malignant lesions[2]. This was principally because of the relatively poor image quality achieved with whole body coils and the inability of MRM to detect microcalcification. Subsequently, advances in scanning techniques and the development of specialized breast coils have allowed the evolution of MRM as a clinically useful investigation.

In brief, the signal required for the generation of an image is produced when hydrogen nuclei, previously aligned in a magnetic field and excited to a higher energy state by the input of electromagnetic radiation (radiowaves), relax back into their resting state. Several magnetic fields are used to provide spatial information and a Fourier transform is used to convert the electromagnetic signal into the image. By varying the length of time before repeating the input of energy or reading the resultant signal, the various T1 and T2 images can be produced. In general, fat is bright on T1 images and water is bright on T2 images. Contrast enhancement became available with the introduction of gadolinium-based contrast agents in the mid 1980s[3]. Chelating the gadolinium to diethylenetriamine penta-acetic acid (DTPA) reduced toxicity while improving osmolarity and water solubility. The normally hyperintense signal produced by the fat within the breast can now be suppressed, which improves the clarity of the image and facilitates the use of such contrast agents[4].

Early studies of simple MRM before and after contrast enhancement demonstrated a markedly increased sensitivity for the detection of breast cancer, although this increase in sensitivity was offset by an associated drop in specificity as some benign lesions, such as fibroadenomas, also enhanced after contrast[3]. Fast scanning techniques were subsequently developed with somewhat amusing acronyms, such as turbo FLASH (fast low-angle shot). These techniques allowed dynamic MRM which employed an analysis of the speed and pattern of enhancement to provide the diagnosis. Benign lesions tend to enhance relatively slowly and homogeneously, while malignant lesions enhance rapidly and heterogeneously[5].

The proponents of simple scanning before and after contrast enhancement have highlighted the problems associated with selection of regions of interest when interpreting dynamic scans[6]. However, recent developments in dynamic scanning have facilitated analysis of the whole tumour rather than specific regions of interest. With these techniques specificities of up to 98 per cent may be achieved, with the sensitivity remaining at around 86 per cent[7].

Today, a full range of diagnostic procedures can be performed using MRM[8]. There are now non-ferromagnetic needles and biopsy guns available for magnetic resonance-guided fine-needle aspiration cytology, core biopsy and preoperative mark up of lesions which are visible only on MRM. In the last of these, however, a radiograph of the lesion after excision cannot be used to ensure that the correct tissue has been removed; a further MRM is required at a later stage for such confirmation.

MRM should provide considerably more diagnostic information than conventional mammography. The scar tissue associated with local breast surgery does not usually enhance significantly with Gd-DTPA and this facilitates the early detection of recurrent cancer[4]. In addition, radiographically dense breasts do not represent a problem for MRM diagnosis because of the fundamentally different method of image acquisition of the latter technique. There is usually no need for the breast to be compressed during MRM unless an interventional procedure is planned and the patient can lie in a comfortable prone position with the breast hanging down within the breast coil. No physical discomfort should be experienced and the only significant psychological problem encountered is that patients with claustrophobia cannot enter the confines of the scanning tube. As there is no ionizing radiation associated with MRM, multiple scans are safe. Also, unlike the iodinated contrast media used in many radiographic examinations, Gd-DTPA causes reactions only extremely rarely and sensitization is not considered to be a significant problem. However, the usual contraindications for MRI still apply.

While more diagnostic information may be gleaned from MRM, such information takes a long time to accumulate and does not come cheap. A routine dynamic scan normally takes between 30 and 40 min, and for interventional magnetic resonance techniques the procedure time may stretch to over an hour. No major alterations to the MRI scanner are required to perform MRM but there are extra costs involved in purchasing the breast coils, interventional equipment and the software required for the specialized scan sequences. Once generated, the basic scans can be interpreted easily, although the more complex analysis of dynamic MRM requires computer technology unavailable outside specialist centres. Even when the capital outlay for the scanner has been met, the cost of basic MRM with and without contrast enhancement alone is still approximately 20 times that of conventional mammography.

MRM will not replace radiographic mammography as a first line investigation because of its greater costs and the restricted availability of suitably equipped scanners. However, evidence suggests that this scanning technique should be used for patients in whom traditional mammography is unhelpful or potentially harmful[9]. This includes young women with a significant genetic risk, those with breast prostheses, those at high risk of recurrent cancer following breast conserving therapy and women for whom the traditional mammogram is equivocal. MRM now offers the reassuring prospect of sensitive and specific breast imaging for these patients, without the risk of exposure to repeated doses of ionizing radiation.

P. J. Drew
J. R. T. Monson

The University of Hull Academic Surgical Unit
Castle Hill Hospital,
Hull HU16 5JQ
UK

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British Journal of Surgery 1996, **83**, 1319–1328

Review

Thirty-five years of isolated limb perfusion for melanoma: indications and results

B. C. VROUENRAETS, O. E. NIEWEG and B. B. R. KROON

Department of Surgery, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Ziekenhuis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

Correspondence to: Dr B. B. R. Kroon

Isolated limb perfusion (ILP) for limb melanoma remains controversial despite its frequent use for over 35 years. To determine whether it has proven benefits, reported results have been reviewed. The value of adjuvant ILP cannot be determined from the multitude of retrospective studies on this subject. Preliminary results of the large European Organization for Research and Treatment of Cancer–World Health Organization–North American Perfusion Group trial suggest that patients with melanomas of 1·5–3·0 mm in thickness who do not undergo elective lymph node dissection may have a locoregional control benefit from ILP. However, as long as a definite survival advantage for ILP has not been demonstrated, such treatment does not seem justified for these patients. The value of prophylactic ILP after resection of recurrent limb melanoma is also scientifically unproven. The potential prevention of further limb recurrence for only a limited period of time, as demonstrated in a rather small Swedish trial, probably does not justify routine use of ILP in these patients; a large international trial will be needed to assess whether ILP provides a survival advantage. For those with locally inoperable limb melanoma, ILP appears to be the treatment of choice since it results in complete disappearance of all macroscopic disease in a substantial proportion of patients, removing the need for amputation and providing palliation of symptoms. However, high limb recurrence rates and short duration of response need improvement. Results of alternative treatments should be compared prospectively with those of ILP in this clinical situation.

In 1957, Creech *et al.*[1] introduced the technique of isolated limb perfusion (ILP) in the treatment of melanoma. The main advantage of ILP is that by isolating a limb from the rest of the body a high dose of cytostatic drug (usually melphalan) can be given locoregionally, thereby minimizing systemic exposure to the drug and subsequent toxicity to vital organs. Isolation of the blood circuit of a limb is achieved by clamping the major artery and vein, ligating collateral vessels and applying a tourniquet around the base of the limb. After cannulation of the vessels, the isolated limb is provided with an artificial circulation by means of an oxygenated extracorporeal circuit, into which the cytostatic drug is injected. For melphalan, the concentration in the perfusion circuit is approximately ten times higher than that in blood at the maximum tolerated dose normally used for systemic administration[2,3]. After a period of isolated circulation, the limb is rinsed with an electrolyte solution, the cannulas are removed and the vessels repaired. Theoretically, the concept of ILP offers therapeutic advantages especially in the treatment of tumours with a relatively high tendency for locoregional recurrence, such as melanoma.

Unfortunately, the value of ILP remains controversial because of the shortcomings of most studies on its use[4–8]. Published results of ILP are typically limited to survival data, lack control groups, frequently contain small numbers of perfused patients, and often describe only a short follow-up. In many studies, the stage of disease and extent of associated surgery are not clearly defined.

In an effort to determine whether ILP has proven benefits, a literature search was performed using MEDLINE, the recent international surgical literature and the bibliography of articles collected. All reports that include a control group of non-perfused patients and/or provide objective response rates are reviewed here.

Prophylactic isolated limb perfusion as an adjuvant to local excision of primary melanoma

In a number of patients melanoma recurs locoregionally because of the microscopic involvement of local tissues, regional lymphatics and soft tissues between the primary and the first major regional nodal basin[5,9–13]. Risk factors for such recurrences are thick primary lesions, ulceration, location of the primary lesion on the sole of the foot or in the subungual tissue, regional node recurrence and inadequate surgical resection margins[5,12,13]. Treating an entire limb in an effort to eliminate these clinically undetectable tumour deposits makes sense, but can ILP really eliminate microscopic metastatic cells not removed by primary surgery and, the main objective, does this improve survival?

In the literature, six retrospective studies[14–21] using historical controls from the reporting institutions' own previous experience could be found. Results were not unanimously in favour of ILP: benefits could either not be demonstrated[14,18] or could be shown only in rather small subgroups of patients with more deeply invasive melanomas[17,19,20]. Some of these studies were performed when important prognostic factors, such as Breslow tumour thickness[22] and Clark level of invasion[23], were unknown. The perfused patients often formed a selected group[14–16,18,19,21,24], especially with regard to age, sex, tumour thickness, associated surgery and location of the primary lesion. In the light of the current knowledge of prognostic factors and more refined statistical techniques, these early studies with historical control groups appear to be of limited use in the assessment of the value of ILP.

Paper accepted 1 June 1996

Four studies[25–29] reported a more proper analysis of the value of ILP in primary melanoma by using matched controls for comparison. However, only one of these studies[28,29] was prospective in design. The pitfalls of using retrospective studies to assess the impact of ILP on outcome were amply illustrated by two reports from the Netherlands[25,26]. A group of patients from Groningen treated with wide excision and ILP with melphalan was retrospectively compared with a similar group of patients from Sydney treated with wide excision only[25]. The study was confined to women with a melanoma of the lower limb with Breslow thickness of 1·5 mm or more and Clark level IV or V; none underwent lymph node dissection. The two groups were similar in age, Breslow thickness, Clark level, ulceration and location of the primary lesion. Women with a melanoma of the leg (excluding the foot), who had been treated by excision and adjuvant ILP, had a significantly better 10-year disease-free survival rate (77 *versus* 45 per cent), a significantly higher 10-year overall survival rate (81 *versus* 60 per cent) and fewer locoregional recurrences (22 *versus* 54 per cent) than women treated by excision only. Curiously enough, for tumours of the foot, no significant benefits were observed from ILP. Subsequently, patients from Groningen were compared with another group of similar matched but non-perfused patients from a nearby region in the Netherlands and Germany[26]. The selection criteria to cross-match these two groups were: tumour location not in proximal third of upper arm or leg; Clark level III to IV; and Breslow thickness of 1·5 mm or more. In contrast to the previous comparison, no effect attributable to ILP was demonstrated in time to limb recurrence, time to regional lymph node metastasis, time to distant metastasis, disease-free interval or survival. This latter study by Franklin *et al.*[26] is theoretically superior to the former as variations in factors such as skin complexion and sun exposure were reduced to a minimum, patient groups were considerably larger and the authors performed a multivariate analysis to correct for all the relevant prognostic factors.

In the USA, 151 patients with primary melanoma treated with wide excision and ILP at the M.D. Anderson Cancer Center, Houston, Texas, were compared retrospectively with a similar matched group of 151 patients who underwent wide excision only at the University of Alabama and the University of Sydney[27]. Patients were individually matched for Breslow thickness, Clark level, site of the lesion and sex. Either of two drugs, melphalan and imidazole carboxamide, was used for ILP. No significant difference in either the disease-free or overall survival rate was found between the groups of patients using either drug. However, in a subgroup analysis of 25 patients with lesions thicker than 2·0 mm on the lower limb treated with wide local excision and ILP with melphalan, a significant improvement in both overall and disease-free survival was found.

In 1993, McKay *et al.*[28] had treated 64 consecutive patients with primary melanoma thicker than 1·5 mm by wide excision and ILP using melphalan since 1984. These patients were prospectively compared with 64 control patients, individually matched for sex, age, site of lesion and Breslow thickness but treated by wide excision alone. Overall survival analysis of both groups revealed no significant difference. However, analysis of patients with lesions of 1·5–3·0 mm in thickness suggested a benefit from ILP in terms of both time to first recurrence and survival. This study was updated in 1995[29], when it contained 120 consecutive patients and 120 individually matched controls. At that time, overall survival analysis of both groups revealed no significant difference. Neither was there a significant difference in survival with respect to sex, age, site or Breslow thickness. Because these matched comparative studies produced conflicting results, the need for prospective randomized trials was obvious[30,31].

In 1984, Ghussen *et al.*[32] reported the first randomized prospective study in which 37 patients with primary melanoma were randomized either to wide excision and regional lymph node dissection or to similar surgery plus ILP with melphalan. The local recurrence rate in the control group was 28 per cent and in the perfused group 5 per cent; this work was updated in 1989[33]. After a median observation time of approximately 6 years, the benefits of ILP (significantly better disease-free and overall survival rates) were again demonstrated[34]. This study has been criticized severely[5,10,30,35,36] for the small number of patients, the high recurrence rate in the control arm and the lack of a multivariate analysis.

A well designed multi-institutional study was conducted by the European Organization for Research and Treatment of Cancer (EORTC) Melanoma Cooperative Group, the World Health Organization (WHO) Melanoma Programme, and the North American Perfusion Group (NAPG) between 1984 and 1994[37,38]. In a prospective fashion, patients with a melanoma of at least 1·5 mm in thickness were randomized to wide excision with ILP or wide local excision alone. The decision to perform elective lymph node dissection was left to local policy. ILP was performed with melphalan, 10 mg per litre of tissue for the lower limbs and 13 mg/l for the upper limbs. Perfusion was done under mild hyperthermic conditions (38–40°C) for a duration of 1 h. After a median follow-up of 4 years, an interim analysis of 813 evaluable patients showed an overall improvement in disease-free interval after ILP ($P = 0·03$), with patients with tumour thickness between 1·5 and 3·0 mm without lymph node dissection benefiting most[39]. In patients without lymph node dissection, the occurrence of in-transit metastases as first sign of progression was reduced from 5·6 to 1·8 per cent and the occurrence of lymph node metastases from 22·6 to 16·6 per cent after ILP. No difference in overall survival could be detected. However, there was a trend towards improvement in survival with ILP for patients with melanomas 1·5–3·0 mm thick ($P = 0·07$); for those with thicker melanomas, there was no difference. For definite conclusions, the final results of this trial are eagerly awaited.

At this moment, ILP seems unjustified for patients with primary melanoma as a survival advantage has not so far been demonstrated. It does not make sense to use a laborious and expensive procedure that carries a definite risk of serious morbidity to prevent or delay locoregional recurrences in only a small percentage of patients. Such recurrences can generally be managed with local excision(s) or therapeutic lymph node dissection. Moreover, the recent emergence of selective lymphadenectomy based on lymphatic mapping presents a novel technique of detecting early lymphatic dissemination[40]. This approach reserves a major operation, i.e. regional node dissection, for only those patients with demonstrated lymphatic metastases. It involves a much less invasive, less morbid surgical procedure than ILP for prevention of clinically involved regional lymph nodes[40–43].

Prophylactic isolated limb perfusion as an adjuvant to excision of recurrent melanoma

The role of adjuvant ILP in recurrent melanoma of the limbs is more easily justified according to many authors[4–6,8,13,35,44–49]. In comparison to the reported 8–50 per cent 5-year survival rate following surgical excision alone for locoregional recurrence of limb melanoma[50], large series suggest that ILP improves survival (28–73 per cent) (*Table 1*)[50–57]. These observations, however, are subject to the criticisms inherent in retrospective analysis without controls; the apparently improved survival may be purely a result of patient selection[5,8,35]. Those receiving ILP possibly form a selected group in which the tumour biology is characterized by a low tendency for systemic manifestation combined with a rather high potential for locoregional recurrence[8,54]. Stringent screening for distant metastases and exclusion of such affected patients from ILP may also have been responsible for the survival benefit[8]. The belief that uncontrollable locoregional disease requiring amputation is seldom seen with ILP[30,35] cannot be substantiated.

A significant number of these patients will fail and again succumb to locoregionally recurrent disease, despite prophylactic ILP[5]. After ILP and resection of all macroscopic tumour tissue, limb recurrence rates are reported to be of the order of 36–50 per cent in large series[51,53,54,56]. The majority of these recurrences occur within 2–3 years of ILP[51,53,54,56], the median duration of the limb recurrence-free interval is between 5 (stage IIIAB) and 9 (stage II) months[54]. On the other hand, meticulous removal of in-transit metastases cures the disease often enough to make it difficult to compare the effectiveness of any adjuvant treatment[24].

In five retrospective comparative studies[14,15,46,58–60] of patients with recurrent melanoma, a significant advantage of ILP over excision alone could not be convincingly demonstrated. In only two of these studies[59,60] did ILP decrease the locoregional failure rate significantly; survival was not affected. Definite conclusions cannot be drawn because the treatment groups were too small, follow-up periods were too short, and the treatment groups were neither homogeneous nor matched for important prognostic factors, such as stage of disease, number of lesions, number of previous limb recurrences, tumour thickness and Clark level of the primary melanoma[54,57,61]. Therefore prospective randomized trials are needed to establish the value of adjuvant ILP in recurrent melanoma[59], just as in the case of primary disease.

In the previously mentioned severely criticized[5,10,30,35,36] studies of Ghussen *et al.*[32] locoregional recurrence rates in the control group were 32 (six of 19) and 59 (ten of 17) per cent for M.D. Anderson stages II and III respectively. In the ILP group analogous values were 6 (one of 18) and 13 (two of 16) per cent. The differences between the groups were significant and persisted after a median observation time of almost 6 years[33,34].

In 1991, the Swedish Melanoma Study Group[62] published the results of a prospective randomized trial involving 69 patients with recurrent melanoma (local recurrence, satellitosis or in-transit metastases). These patients were randomly allocated to radical surgery (36 patients) or radical surgery plus ILP with melphalan and limb temperatures of 40–41·5°C (33 patients). Stratification was employed for localization to an upper or lower limb. With a mean observation time of 39 months, the tumour-free survival time was enhanced in the ILP group from 10 to 17 months ($P = 0{\cdot}04$). The type of recurrence was similar in both groups, but further recurrences within the limb were fewer in the ILP group: six *versus* ten local recurrences, six *versus* nine in-transit metastases and three *versus* five regional lymph node metastases. Again, an overall survival advantage could not be demonstrated ($P = 0{\cdot}28$). The authors concluded that ILP cannot be recommended except in prospective randomized studies with a non-perfused control arm[62,63]. Because these future studies must achieve prolonged survival, large international trials will be needed[62].

Therapeutic isolated limb perfusion in locally advanced melanoma

With the advent of ILP, the need for amputation to control extensive limb melanoma has been reduced substantially[4,6,8,10,35,51,64–69]. Nowadays, such ablation is required only rarely for extensive or deeply infiltrative lesions associated with severe pain, bleeding and odour

Table 1 Five- and 10-year survival rates after local surgery with or without prophylactic isolated limb perfusion in patients with locoregionally recurrent melanoma of the limbs

Reference	Year	No. of patients	5-year survival (%) II	5-year survival (%) IIIA	5-year survival (%) IIIAB	10-year survival (%) II	10-year survival (%) IIIA	10-year survival (%) IIIAB	Limb recurrence rate (%)
Local surgery									
Treidman and McNeer[50]	1963	75	—	50*	8	—	—	—	—
Local surgery and ILP†									
Rosin and Westbury[51]	1980	116	—	—	—	—	—	—	50
Stehlin *et al.*[52]	1988	117	75	70	36	—	50	23	—
Baas *et al.*[53]	1988	110	74	67	40	63	45	34	38
Klaase *et al.*[54]	1994	216	57	45	25	—	—	—	45
Krementz *et al.*[55]	1994	324	80	36	23	61	30	17	—
Cavaliere *et al.*[56]	1994								
Rome		112	80‡	54	21	—	54	21	49
Milan		215	—	46	33	—	26	19	36
Mean		—	73	48	28	62	37	21	43

M.D. Anderson staging system for melanoma: II, local recurrence/satellitosis; IIIA, in-transit metastases (3 cm or more from primary lesion, scar or skin graft); IIIAB, in-transit and regional lymph node metastases. *II and IIIA. †Only series of more than 100 patients are listed; ‡Di Filippo *et al.*[57] (1989). ILP, isolated limb perfusion

Table 2 Complete response rates in patients with melanoma after isolated limb perfusion with melphalan

Reference	Year	No. of patients	Complete response rate (%)	Tissue temperature (°C)	Limb recurrence rate (%)*
1966–1988					
Irvine and Luck[75]	1966	10	40		50
Cox[58]	1975	19	53	40†	40
Hansson *et al.*[76]	1977	14	21	40–42†	
Jönsson *et al.*[77]	1983	15	7	> 38	
Rosin and Westbury[51]	1980	80	26	39–40	
Lejeune *et al.*[78]	1983	23	65	39–41	
Minor *et al.*[79]	1985	22	81	40	
Storm and Morton[80]	1985	26	81	40·5–42	24
Mean complete response rate (1966–1988)			44		
1988–1995					
Hohenberger[21]	1990	41	49		
Kettelhack *et al.*[71]	1990	35	60	39–40	
Neades *et al.*[72]	1991	17	76	39	47
Kroon *et al.*[81]	1992	11	64	41–42	
Kroon *et al.*[82]	1992	10	90	42–43‡	
Mattson *et al.*[83]	1992	70	36	40	
Cavaliere *et al.*[56]	1994				
Rome		112	44	41–41·8	49
Milan		138	59	41–41·8	36
Klaase *et al.*[61]	1994				
Single		73	44	37–38	46
Multiple		47	70	37–38	
McKay *et al.*[84]	1994	49	39	39–40	
Thompson *et al.*[85]	1995	104	73	40–41	54
Lejeune[86]	1995	103	52	37–40	
Bryant *et al.*[87]	1995	85	40	41·5	
Mean complete response rate (1988–1995)			54		
Mean local recurrence rate (1966–1995)					44

Only series of ten or more patients are included. *In patients with complete remission; †temperature of heat exchanger; ‡hyperthermia and melphalan sequentially

not responding to ILP[68,69]. Although the main indication for ILP has traditionally been in-transit metastases not amenable to local surgery[6,8,24,31,35,70–72], data on objective response rates in large series are scarce[35,73,74]. All series in the literature that contained at least ten patients with measurable disease are summarized in *Tables 2–4*. Most data apply to recurrent disease; some include neglected primaries.

With ILP using melphalan, a mean complete remission rate of about 54 per cent can be obtained nowadays (*Table 2*). Complete remission rates have tended to improve over the years. ILP at the beginning of the perfusion era was associated with lower remission rates and complete remission rates have increased by approximately 10 per cent since 1988[35]. This may be attributed not only to the fact that most of the early ILPs were probably performed under less effective hypothermic conditions[35] but also because ILP schedules have become more sophisticated[35,74]. After ILP with melphalan, irrespective of tissue temperature, the median duration of complete remission ranges between 9 and 19 months, depending on the follow-up period[61,78]. In patients with complete remission, further limb recurrence develops in approximately 44 (range 24–54) per cent (*Table 2*) after a relatively short median interval of 5–10 months[57,61,72,85,102].

Strategies have been developed to improve the complete remission rate, such as multiple ILP schedules, application of hyperthermia, use of cytostatic agents other than melphalan and the introduction of biological response modifiers[74]. It is interesting to note that the complete response rates of 'controlled' normothermic ILP (tissue temperature between 37 and 38°C) and of ILP performed under 'mild' hyperthermic conditions (39–40°C) are within the same wide range (39–76 per cent)[61,71,72,84,86]. Only by using borderline 'true' hyperthermia (41–42°C)[57,80,81] or multiple ILP[103] do these complete response rates seem to improve significantly. No other drug is as effective as melphalan in the ILP setting, either as a single agent or in a multiple agent regimen (*Table 3*)[35,47,74].

A promising new development is the introduction of recombinant tumour necrosis factor (TNF) α to ILP (*Table 4*). The combination of this agent with interferon (IFN) γ and melphalan was first used by Lejeune's group in Brussels[96,104]. Complete remission was achieved in 17 of 19 patients with melanoma treated for stage IIIA or IIIAB disease, with the majority having five or more melanoma nodules after failure of previous ILP with either melphalan or cisplatin[96,104]. In a multicentre study[97], response rates from ILP with the combination of TNF-α, IFN-γ and melphalan remained high, with a complete remission rate of 91 per cent in 53 patients with stage

IIIA (34 patients), IIIAB (15) and IV (four) disease. After a median follow-up of 26 months, limb recurrence was observed in 21 (40 per cent) of these 53 patients, with a median duration of response of 14 months[86,97]. The mean number of lesions was 25, and 48 patients had more than five nodules. These response data were compared with those of 103 patients with similar stage III regionally recurrent melanoma, who were treated with standard melphalan ILP between 1980 and 1988 by the same teams[86]. Melphalan ILP alone produced a significantly lower complete response rate (52 per cent); in a multivariate analysis, the difference in complete response rates remained significant. However, although the median response duration has not yet been reached, the means were comparable: 3·9 years for patients receiving melphalan alone and 3·6 years for those receiving TNF-α, IFN-γ and melphalan[86]. Whether the addition of IFN-γ is necessary to achieve the 90 per cent complete remission rate is being addressed currently in a randomized phase II study[98]. Preliminary results show an 84 per cent complete remission rate in 31 patients after the triple regimen compared with 61 per cent in 33 patients when IFN-γ was omitted[98].

Data from similar recently reported trials from Italy have not confirmed these impressive findings (*Table 4*)[99,100,105–107]. Complete response rates with TNF-α, with or without IFN-γ, were 50–70 per cent[99,100,105–107] and most patients did not present with bulky disease as treated by Liénard *et al.*[97]. Regional relapse rates ranged from 15 to 50 per cent[100,105–107], with relapses occurring after only a short median period of 6 (range 3–14) months following ILP[100,105,107]. These figures and the Italian results after 'borderline' hyperthermic (41–42°C) ILP with melphalan alone were considered to be essentially the same[46,49,56,99,107], although the short follow-up of the TNF-α series does not allow any definite conclusions to be drawn[107]. Currently, the Surgery Branch of the National Cancer Institute, Bethesda, Maryland, is conducting a trial comparing the combination of TNF-α, IFN-γ and melphalan with melphalan alone in ILP[108].

Progress is allowing the ideal of a 100 per cent complete remission rate to be approached in several series[82,96,97,104]. However, most of these studies have a relatively short follow-up, without mention of the long-term durable complete response rate. In the few studies that do supply this information, the limb relapse rate after a complete remission is a disappointing 40 per cent and the corresponding limb disease-free interval is of only a short duration. It also remains difficult to assess what proportion of patients with irresectable melanoma can obtain good palliation with ILP, as most reports do not indicate whether responses were obtained in locally inoperable melanoma or, as probably was the case in many series, in recurrent disease deliberately left *in situ* to monitor the effect of ILP. Because the macroscopic tumour burden (as expressed by number of lesions, total tumour surface area and nodal status) is an important prognostic factor for tumour response and limb recurrence-free interval[57,61], these local control rates are probably too optimistic for patients with locally inoperable melanoma.

Toxicity and morbidity associated with isolated limb perfusion

Standardization of ILP technique and technological improvements have permitted a reduction of the most serious complications to a minimum[46,49]. Slight oedema, skin erythema and pain in a warm limb commonly occur approximately 48 h after ILP, and usually resolve within 14 days[49,109,110]. The redness fades to brown, which gradually becomes lighter over a period of 3–6 months; there is usually no visible abnormality after approximately 6 months. Other local manifestations, e.g. temporary loss of nails, drying or blistering of skin of palms of the hands or soles of the feet, and inhibition of hair growth on the limb, are sometimes seen[109,110]. From published data of large series one may conclude that more severe acute skin and soft tissue reactions (ranging from pronounced erythema and/or oedema associated with some blistering to, rarely, compartmental compression syndromes and reactions necessitating amputation) are seen in 7–37 per cent of perfused patients[111,112]. Factors that predispose to a more severe reaction are tissue temperature of 40°C or higher, female sex, deterioration of blood gas values of the perfusate, proximal isolation level, low flow rate, and pharmacokinetic parameters, such as high total melphalan dosage, high melphalan peak concentration, high concentration at equilibrium and a large area under the curve[111–114]. When these factors are taken into account,

Table 3 Complete response rates in patients with melanoma after isolated limb perfusion with drugs other than melphalan

Reference	Year	No. of patients	Complete response rate (%)	Drugs
Cox[58]	1975	28	36	Thiotepa, melphalan
Golomb[88]	1976	54	13	Thiotepa, actinomycin D, melphalan
Aigner *et al.*[89]	1983	12	17	Cisplatin
Aigner *et al.*[90]	1984	14	0	Vindesine, dacarbazine, cisplatin
Shiu *et al.*[91]	1986	19	32	Nitrogen mustard
Vaglini *et al.*[92]	1987	24	13	Dacarbazine
Coit *et al.*[93]	1988	12	0	Mouse monoclonal antibody R24
Coit[94]	1993	24	33	Cisplatin
Vaglini *et al.*[95]	1995	10	10	Interleukin 2 and LAK cells

Only series of ten or more patients are included. LAK, lymphokine-activated killer

Table 4 Complete response rates in patients with melanoma after isolated limb perfusion with melphalan, tumour necrosis factor α and interferon γ

Reference	Year	No. of patients	Complete response rate (%)	IFN-γ	Limb recurrence rate (%)*
Liénard *et al.*[96]	1992	29	90	Yes	
Liénard *et al.*[97]	1994	53	91	Yes	33
Liénard *et al.*[98]	1995	31	84	Yes	
		33	61	—	
Santinami *et al.*[99]	1995	47	57	In 12	
Di Filippo *et al.*[100]	1995	10	50	—†	
Fraker *et al.*[101]	1996				
TNF-α 4 mg		25	76	Yes	53
TNF-α 6 mg		11	36	Yes	25

Only series of ten or more patients are included. *In patients with complete remission; †temperature 41°C or more. TNF, tumour necrosis factor; IFN, interferon acute limb toxicity after ILP should be mild nowadays. This is extremely important as a strong correlation has been demonstrated between acute regional toxic reactions and the incidence of long-term morbidity, especially in the form of muscle atrophy/fibrosis and limb malfunction, which occurred in 11 and 15 per cent respectively of 367 patients at 1 year after ILP[115]. Only two other studies[116,117] focused on the issue of long-term morbidity, with conflicting results. In one report[117], no additional morbidity was noted after 'mild' hyperthermic (38–40°C) ILP compared with wide excision alone. In the other study[116], objective investigation after a median follow-up of 5 years after normothermic (37–38°C) ILP noted oedema or atrophy in three of 15 upper limbs and 15 of 42 lower limbs. The ankle proved to be particularly vulnerable with restriction of movement in more than 25 per cent of cases[116].

Mortality rates after ILP with melphalan range from 0 to 9 per cent[118], with deaths mainly reported in the beginning of the ILP era. Death usually resulted from pulmonary embolism, cardiac failure, renal failure or bone marrow depression. This last side-effect is reported to occur to some extent in up to 59 per cent of perfused patients[118] and is strongly associated with leakage of cytostatic drug into the systemic circulation[6,46,71,72,119], especially during the first 5–10 min of perfusion[72,119]. Systemic toxicity is negligible in the absence of significant leakage. Nausea and vomiting seem somewhat more pronounced after ILP than after other surgery of the same duration and extent[75,118,120]. It has been suggested that the combination of melphalan, anaesthetic agents, major surgery and postoperative narcotic analgesics may be a powerful emetogenic stimulus[120].

In contrast to the negligible incidence of severe systemic side-effects after modern ILP with melphalan, the complications associated with TNF-α in ILP can be impressive. Leakage of TNF-α, which unlike melphalan maintains a high stable drug level in the perfusate throughout ILP[104], can induce a systemic inflammatory response syndrome comprising fever and chills, hypotension and adult respiratory distress syndrome[97,104,105]. However, this toxicity can also be almost completely prevented by adequate control of leakage and extensive washout procedures at the end of perfusion[86,97,121,122].

Alternative methods of locoregional disease control

Since ILP was first described, attempts have been made to achieve similar results more simply using other regional chemotherapeutic techniques. Intra-arterial infusion of cytostatic agents and 'tourniquet infusion' with partial venous outflow occlusion are examples[123]. However, no other method has produced remission rates comparable to those of ILP. Recently, isolated limb infusion (ILI) has been developed as an alternative technique which is simpler than ILP[124]. Arterial and venous catheters are inserted percutaneously into the limb and a pneumatic tourniquet is inflated proximally. The cytostatic drug (melphalan), in 300–400 ml warmed saline, is infused rapidly through the arterial catheter. For 15 min it is continuously circulated via a simple warming coil by aspiration from the venous catheter and re-ejection into the arterial catheter, using a syringe and three-way tap. Of 12 patients treated by ILI, complete remission was obtained in six and partial remission in the rest. However, all complete responders experienced recurrence in the limb after a median interval of 11 months. Because of the simplicity and low morbidity, a routine double ILI protocol is currently being considered[124].

Local excision of individual lesions is impractical when they are numerous, large or recurring with a short disease-free interval[125–128]. Other methods of local ablation such as diathermy or cryosurgery may be used, but their efficacy has not been reported. Moreover, these techniques are not precise and a wide margin of normal tissue must be destroyed to ensure tumour necrosis. Carbon dioxide laser ablation of cutaneous metastases of melanoma has been described recently[125–129]. Because of its wavelength, carbon dioxide laser radiation is highly absorbed by soft tissues and so dissipation of heat to surrounding tissues by conduction is reduced, thus minimizing thermal damage. In a typical case ten to 15 lesions can be ablated under local anaesthesia in 15 min, but up to 450 lesions have been treated at one time. Recurrence at lasered sites is rare but, in any event, laser therapy can be repeated several times for subsequent recurrences with little morbidity. Its major benefit is that it can be carried out with little disruption to the patient's normal way of life. It is, however, important to appreciate that laser treatment is not suitable for all patients, particularly those with deep subcutaneous nodules or plaques, ulcerated or fungating lesions, and lesions larger than 1·5 mm in diameter.

Systemic chemotherapy, immunotherapy and local radiotherapy are of only limited effectiveness[130]. However, the addition of hyperthermia to radiotherapy in large doses per fraction has been reported as improving local tumour control with a complete response rate of 62 per cent (compared with 35 per cent using radiotherapy alone) with an acceptable level of complications[130]. The treatment consisted of three fractions at intervals of 4 days followed within 30 min by hyperthermia (43°C). Also, large nodules (greater than 4 cm) can be treated effectively; only 15 per cent of the 103 tumours that showed complete or partial responses regrew after a median response time of 10 months. This treatment combination is, however, suitable only for single or a few metastatic nodules. It is not yet widely available[131].

Conclusion

The major problem in assessing the true value of ILP in the management of melanoma is the lack of prospective randomized trials. In patients with 'high-risk' primary melanoma, preliminary results from the large international EORTC–WHO–NAPG trial showed a possible locoregional control benefit in those with lesions between 1·5 and 3·0 mm in thickness who did not undergo elective lymph node dissection. However, as long as a definite survival advantage has not been demonstrated, ILP does not seem indicated in patients with primary melanoma.

In the only available prospective randomized trial involving patients with recurrent limb melanoma, ILP delayed the occurrence of locoregional metastases, compared with excision of recurrences alone. Again, because no survival advantage was shown, a large international trial comparing ILP with simple excision or laser ablation is necessary to establish the value of ILP for this indication.

In patients with recurrent limb melanoma that is not suitable for local treatment, ILP is the treatment of choice. For this indication, ILP results in the complete disappearance of all macroscopic disease in a substantial proportion of patients, thereby palliating symptoms and removing the need for amputation. With modern perfusion techniques, limb and systemic toxicity is usually mild. However, the high limb recurrence rate and short duration of response need improvement. Results of alternative treatments should be compared prospectively with those of ILP in this clinical situation.

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British Journal of Surgery 1996, **83**, 1329–1334

Review

Vascular complications of injecting drug misuse

K. R. WOODBURN and J. A. MURIE

Vascular Surgery Unit, The Royal Infirmary, Edinburgh, UK
Correspondence to: Mr K. R. Woodburn, Vascular Surgery Office, Department of Surgery, University of Edinburgh, The Royal Infirmary, Edinburgh EH3 9YW, UK

Drug misuse is now a significant problem in western society; many different pharmaceuticals are administered by drug abusers as intravenous preparations. This has resulted in an increasing number of complications associated with prolonged intravascular and perivascular injection of abused substances. These complications of intravenous drug abuse may lead to limb-threatening arterial injuries that present a considerable management problem in patients who often have significant co-morbidity. This article provides a comprehensive review of the vascular complications that result from drug misuse by injection. It discusses the aetiology and clinical features of these complications and highlights the limited role of both the general surgeon and specialist vascular surgeon in the management of these patients.

The number of injecting drug abusers in the UK is unknown, but a random survey carried out in Scotland of 5000 adults between the ages of 15 and 59 years indicated that just under 1 per cent of this age group have injected drugs at some time[1]. In the Edinburgh urban area the prevalence of currently injecting drug abusers in the same age group is estimated at four per 1000 (95 per cent confidence interval (c.i.) 3·0–5·5 per 1000), the rate doubling if addicts who have injected at any time in their drug abusing career are included (Davies AG, personal communication). The relatively large number of injecting drug abusers has led to increased recognition of arterial and venous complications associated with the parenteral administration of abused drugs and, although most general surgeons encounter these problems infrequently, they present considerable difficulty in diagnosis and management, particularly in regions where there is a high prevalence of human immunodeficiency virus (HIV) infection in the drug abusing population. The prevalence of HIV infection in injecting drug addicts in Scotland ranges from 0·8 per cent in Glasgow[2] to 19·7 (95 per cent c.i. 15·5–23·9) per cent in the Edinburgh area[3].

The vascular complications of drug abuse tend to occur after prolonged drug administration leading to an absence of easy peripheral venous access because of the phlebitis associated with repeated non-sterile injection. The addict eventually attempts to administer drugs into a major deep vein, commonly in the groin, with a substantial probability of vascular injury occurring. This may take the form of direct intra-arterial injection which can lead to limb ischaemia, either primarily as a consequence of direct local arterial injury and occlusion or as a result of distal small vessel damage, depending on the nature of the preparation used. Infective vascular complications may also result, such as pseudoaneurysm, which may arise after repeated perivascular and intravascular injection of non-sterile preparations.

Intra-arterial injection

Accidental intra-arterial injection resulting in limb ischaemia and tissue necrosis was first reported in relation to the medical administration of parenteral preparations of the barbiturate thiopentone[4,5]; similar sequelae have been reported following intra-arterial injection of oral barbiturate preparations in intravenous drug addicts[6,7]. Limb ischaemia and tissue necrosis in drug abusers have subsequently been reported after intra-arterial injection of oral preparations of a wide variety of drugs[8,9], including a recent series of cases associated with the use of 'abuse-resistant' temazepam gel capsules[10–12].

Clinical features

Despite the wide variety of pharmaceuticals involved, including parenteral formulations administered under medical supervision as well as addict-prepared solutions of crushed tablets or powder, liquid contents of capsules and solid gel preparations, the clinical features reported in most cases of intra-arterial injection are remarkably similar. Initially the patient has an intense 'burning' pain in the distribution of the artery injected; this occurs immediately following intra-arterial injection[5–8,10–16]. Although the pain may be accompanied by a hyperaemic flush in the same region[14], drug abusing patients rarely present to hospital at this early stage. The initial symptoms are followed within a few hours by a constant pain and patchy mottling of the affected limb, consisting of areas of pallor and purplish erythema with cyanosis of the digits, together with marked swelling of the limb (*Fig. 1*). The patchy mottling may be observed in tissue proximal to the site of intra-arterial injection. Pain is exacerbated by any movement of the affected limb and, although at this early stage there is no demonstrable neurological deficit, limb swelling can lead to the development of a compartment syndrome and rhabdomyolysis[5–8,10–13] (*Fig. 2*). Most patients have pulses in the affected limb, despite the clinical picture of patchy ischaemia; the subsequent development of tissue necrosis and gangrene is a variable event[5–12] (*Fig. 3*).

Aetiology and pathology

Inadvertent intra-arterial injection of thiopentone during the induction of anaesthesia was thought initially to produce symptoms as a result of thrombosis within the injected vessel, secondary to intimal damage caused by the

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high pH of thiopentone in solution. This was considered to be accompanied by marked distal arteriolar and venous spasm, and diffuse venous thrombosis leading to muscle ischaemia and limb swelling, with eventual tissue necrosis and limb loss[5]. Some animal studies using a rabbit ear preparation support this pattern of marked acute venospasm with venous thrombosis, together with patchy arterial spasm and intra-arterial thrombosis, following injection of thiopentone[17,18]. However, the arterial effects observed in these studies may actually have been related to the design of the experimental model, and other animal studies have indicated that intra-arterial injection of a number of commonly abused drugs fails to produce any significant arterial spasm, and has a vasodilatory effect in most instances[19,20].

It is of interest to note that major tissue loss following intra-arterial injection of barbiturates occurs only in patients in whom one or more major vessel is occluded, as determined either angiographically or by clinical examination[5–7]. In these patients thrombosis and occlusion take place at the site of injection, often several days later, presumably reflecting direct local intimal damage at the time of injection, as postulated by Cohen[5] and supported by the animal studies of Williams and Montgomery[21]. Undoubtedly the limb swelling observed in such patients occurs as a consequence of ischaemic muscle necrosis (*Fig. 4*), while the limb mottling reflects local venous stasis following acute arterial occlusion.

In most patients, however, intra-arterial injection of barbiturates and other drugs is accompanied by a full complement of distal pulses and all the clinical features of

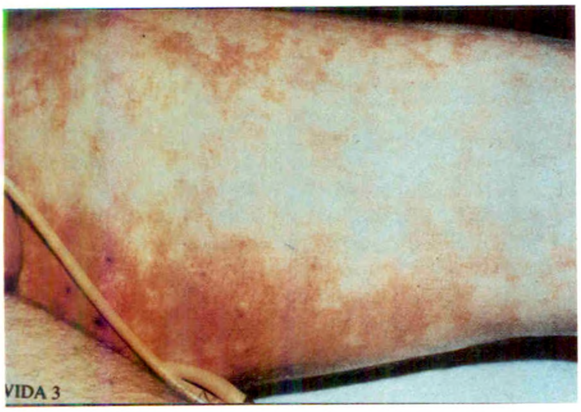

Fig. 1 Characteristic early mottling of the thigh following inadvertent injection of temazepam gel into the femoral artery

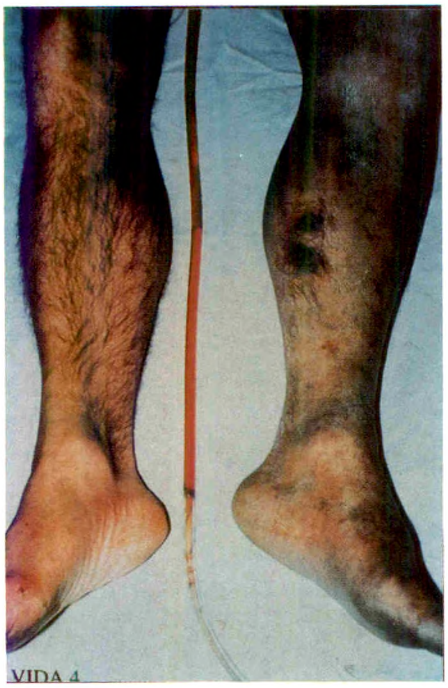

Fig. 2 A painful, tense, mottled limb following intra-arterial injection of temazepam gel. The tube draining the urinary catheter shows myoglobinuria due to rhabdomyolysis. This patient underwent thigh and calf fasciotomy shortly after this picture was taken

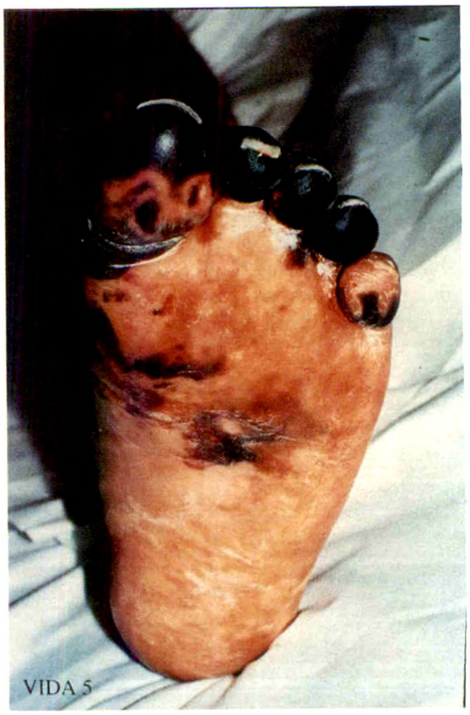

Fig. 3 Development of digital gangrene several days after intra-arterial injection into the right femoral artery

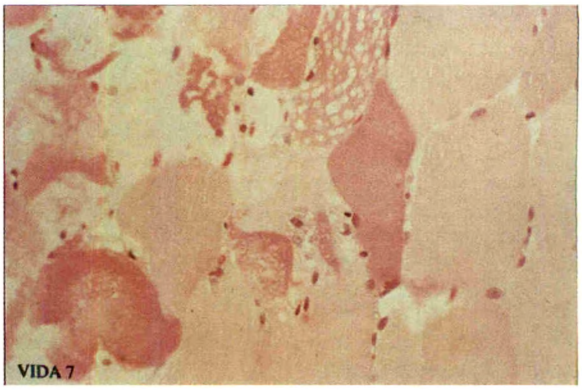

Fig. 4 Histological appearance of a muscle biopsy obtained at the time of fasciotomy following intra-arterial injection of temazepam gel. The patchy vacuolation of myocytes can be seen, with viable myocytes alongside. (Haematoxylin and eosin stain, original magnification × 120)

intra-arterial injection already described[5–13]. Despite the absence of major vessel occlusion there is no doubt that some of the inert components, such as corn starch and talc, which are commonly present in the drug addicts' preparation, can produce transient vasospasm and particulate microemboli leading to microvascular occlusion[7,8,19,20]. This is supported by the observation that particulate microemboli are found in the pulmonary circulation after intravenous injection of abused drugs[22,23]. Spasm in smaller digital vessels has been shown angiographically following intra-arterial injection of temazepam gel[12]. While these features undoubtedly contribute to the clinical presentation, there is evidence that the damaging effects of intra-arterial injection may also be related to venospasm and venous thrombosis[5,13,17], together with a diffuse chemical arteritis as a consequence of endothelial injury[18,21,24].

The overall effects of intra-arterial injection probably arise as a combination of particulate emboli, vasospasm in distal vessels, and endothelial injury leading to small vessel vasculitis and venous thrombosis. These changes produce a picture of diffuse tissue ischaemia, which may be exacerbated if the patchy muscle necrosis that results[11,24] leads to the development of a compartment syndrome with major muscle necrosis. It is this predominantly small vessel and venous damage that gives rise to the clinical picture of limb mottling and swelling with muscle tenderness, in the presence of a full complement of pulses. On the other hand, in the few patients who present with an absent major limb pulse at the site of injection, the postulated mechanism is one of thrombosis following direct mechanical and chemical injury of the vessel at the time of injection[5,21].

Treatment and outcome

In spite of the relatively constant clinical features following intra-arterial injection, the heterogeneity of compounds injected, the small numbers seen by individual clinicians, and the difficulties inherent in treating and following up this difficult group of patients have resulted in a wide variety of putative treatment regimens. Nevertheless, both the requirement for surgical intervention and the eventual outcome are remarkably similar in most series (*Table 1*). There is general agreement, unless major proximal limb pulses are absent, that investigation with a view to reconstructive vascular surgery is not indicated[9,12]. Some authors have attempted a stellate ganglion block following intra-arterial injection in the upper limb but this has not been found to be of benefit[13,15]. The role of fasciotomy is unclear but, in view of the common features of widespread patchy muscle necrosis and tissue oedema[11,24], it may be of some value in the lower limb to prevent renal failure from rhabdomyolysis[10,11], and in the upper limb to prevent subsequent ischaemic contracture[15,25]; however, rhabdomyolysis is likely to result from microvascular thrombosis and subsequent ischaemic muscle necrosis rather than be secondary to a rise in compartment pressures. As *Table 1* indicates, few series of intra-arterial injection reported a high incidence of renal failure, suggesting that fasciotomy should be withheld unless compartment pressure monitoring demonstrates a rise in compartment pressure accompanied by the clinical features of a compartment syndrome. This policy was employed successfully in three cases of upper limb intra-arterial injection reported by Silverman and Turner[26].

Most authors stress the use of intravenous heparin to prevent propagation of intravascular thrombus and to maintain patency of collaterals[5,9,12–15]. This is probably appropriate in view of the extensive arterial and venous thrombosis observed in both animal and pathological studies[13,17,18,24]. Heparin therapy should be continued until limb swelling, pain and mottling have subsided[14], usually between 5 and 10 days after injection[12–14], although in this group of patients early self-discharge often supervenes before this. There is little evidence to support the use of either intra-arterial vasodilators[14,15] or prostacyclin infusion[12], presumably because of the transient nature of the vasospasm that follows intra-arterial injection[17,19,20], although encouraging results following treatment with the prostacyclin analogue, Iloprost, have been reported in one small series[27]. Intra-arterial thrombolysis has rarely been applied in this situation and is, in any event, likely to be difficult to sustain in a group of patients who commonly discharge themselves early from hospital against medical advice[9,14]. Silverman and Turner[26], however, have reported encouraging results after treating a small number of complications of intra-arterial injection using this method.

Supportive medical therapy is, therefore, the best treatment in patients with a full complement of limb pulses following intra-arterial injection. Analgesia should be administered if required, careful monitoring of renal function should be carried out and the patient should be systemically heparinized. Although venous access may require insertion of a central venous catheter in these patients, invasive surgical procedures are rarely indicated, with the exception of fasciotomy in selected cases. Rarely a patient will present with absent proximal limb pulses in the presence of a salvageable limb and in this situation investigation is needed with a view to vascular reconstruction.

Table 1 Outcome following inadvertent intra-arterial injection of abused drugs

Reference	Year	Substance injected	No of cases	Fasciotomy	Renal failure	Major limb amputation	Digit amputation
Gaspar and Hare[13]	1972	Barbiturate	Arm 19	0	0	0	6
		capsules	Leg 1	0	0	0	1
Maxwell *et al.*[14]	1972	Various	Arm 9	0	0	0	3 (debrided only)
		analgesics	Leg 4	0	0	1	2
Stonebridge *et al.*[9]	1990	Analgesic	Arm 2	0	0	0	1
		tablets	Leg 6	0	1	1	0
Scott *et al.*[10]	1992	Temazepam	Arm 5	1	0	1	1
		gel	Leg 10	10	4	1	2
Nott *et al*[12]	1993	Temazepam	Arm 5	0	0	1	4
		gel	Leg 6	0	0	0	1 (debrided only)

Infective vascular complications

A wide variety of infective complications arising as a consequence of poor aseptic technique and parenteral injection of non-sterile preparations in injecting drug abusers has been documented[15,22,28]. It is a commonly held belief that superficial thrombophlebitis and deep vein thrombosis are prevalent in injecting drug addicts[22], although these complications rarely present to surgeons, and their occurrence is poorly documented in the literature. Nevertheless one recent report suggested that as many as 40 per cent of admissions following intravenous temazepam misuse were for deep vein thrombosis[29]. There are, however, some local vascular complications related to infection that are more likely to present to the general or vascular surgeon.

Infected venous pseudoaneurysm

Venous pseudoaneurysm is an infrequently reported complication of injecting drug misuse. In a retrospective review of 172 cases of arterial injury associated with drug injection, Benitez and Newell[16] reported ten venous pseudoaneurysms and 134 arterial pseudoaneurysms; two venous pseudoaneurysms were reported in 32 vascular complications of drug injection reported by Yeager *et al.*[30] There are no reports of venous pseudoaneurysm at sites other than the common femoral vein. In 1984, Johnson *et al.*[31] commented that pseudoaneurysms develop after septic phlebitis of the vein induced by repeated injection under non-sterile conditions. It was suggested that some cases arise when the infected vein ruptures and the communication into the infected haematoma fails to close. Alternatively, in some instances the pus-filled vein may communicate with surrounding tissue via the venepuncture site. Regardless of the exact aetiology of the condition, the diagnosis of venous pseudoaneurysm is usually made at operation in a patient who presents with groin pain, fever, leucocytosis and, sometimes, a fluctuant groin mass[16,31]. Preoperative investigation rarely enables the diagnosis to be made before surgery[16], which consists of excision of the infected pseudoaneurysm with excision and ligation of the infected common femoral vein[16,31]. In view of the high incidence of bacteraemia in these patients, systemic antibiotic therapy should be commenced on admission. The organisms isolated in such patients include *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus* spp.[16,31] but, in view of the manner of preparation of injections by addicts and the high incidence of HIV infection in some addict populations[3], it seems prudent to ensure broad-spectrum cover until bacteriology results become available.

Arterial pseudoaneurysm

First reported in injecting drug misusers in the 1960s[32], infected pseudoaneurysm or 'aneurysmal abscess' has become one of the commonest vascular complications found in drug addicts[14–16,30]. Although infected pseudoaneurysm in this patient population is reported to occur in brachial and radial arteries[16,33,34], the majority of infected pseudoaneurysms associated with injecting drug misuse develop in the femoral artery[16,30,33–38].

Pseudoaneurysm commonly presents as a painful swelling, with fever and leucocytosis also prevalent[16,34], although it may present with intermittent bleeding[35] and, occasionally, massive haemorrhage[31,36,37]. The typical features of an indurated, erythematous swelling may be mistaken for a simple abscess on initial presentation[33], but the majority of pseudoaneurysms are pulsatile on examination, with an audible bruit over the swelling[16]. Nevertheless, since up to 23 per cent of pseudoaneurysms are non-pulsatile[16], careful clinical examination and a high index of suspicion are required in the assessment of any infected groin swelling in an injecting drug addict. Misguided attempts at incision and drainage of a presumed 'abscess' must be avoided.

Drug addicts presenting with infected swellings in the vicinity of a major vessel should undergo duplex ultrasonography to determine whether or not the lesion contains flowing blood, confirming the diagnosis of pseudoaneurysm. Although the use of ultrasonography is not universally advocated[37] and it may lead to a false-negative diagnosis[16], there is little need to carry out routine arteriography unless diagnostic doubt exists[35]. The high incidence of positive bacteriological cultures from both systemic blood and the aneurysm itself, with *Staphylococcus* and *Pseudomonas* occurring commonly[16,33,38], and a significant likelihood of mixed infection[37], make broad-spectrum antibiotic therapy mandatory. The infective risks to operating theatre personnel posed by injecting drug users[3,39] may be reduced by adequate operative exposure of involved vessels; early proximal and distal control of arteries and veins is the safest technique[33,39].

There is no doubt that infected pseudoaneurysm is one of the few indications for vascular surgical intervention in injecting drug addicts. The most appropriate form of intervention for femoral false aneurysm has, however, been the subject of some debate, especially regarding whether or not revascularization should be carried out in all cases at the time of wide surgical debridement of the cavity and ligation of the involved vessels[37,38,40]. Infected pseudoaneurysms of the upper limb vessels seem to require neither revascularization nor amputation after excision and ligation[16,33] (*Table 2*).

Revascularization following ligation and resection of an infected femoral aneurysm often requires the use of a synthetic graft because of the lack of good quality vein in drug abusers[38]. This has been associated with a significant incidence of graft infection and occlusion[36,39], although in many cases occlusion of the graft does not lead to limb loss[39]. A policy of excision and ligation of the aneurysm, with subsequent revascularization where there is postoperative evidence of limb threat, has been advocated by some authors[33,37] as a means of reducing the number of revascularization procedures. This is particularly suitable for patients who undergo common femoral artery ligation alone, which is associated with a low risk of subsequent amputation[37], and the overall limb salvage rates reported after compulsory revascularization are no better than those reported following a policy of selective revascularization (*Table 2*). Most authors report a higher risk of limb threat following ligation of all three groin vessels (common, superficial and deep femoral)[33,35,37]; however, even in this group of patients only a small minority require revascularization[35,37], although most will develop claudication[35]. The overall risk of limb loss after surgery for infected femoral pseudoaneurysm is approximately 10–20 per cent[16,37], although in cases requiring triple femoral vessel ligation this may be as high as 33 per cent[37].

Where revascularization is required it has been suggested that remote iliofemoral bypass using either the

Table 2 Outcome following surgery for infected false aneurysm arising in intravenous drug abusers

Reference	Year	Site of aneurysm excision	No. of cases	Revascularization policy	Primary amputation (no graft)	Bypass grafting	Amputation following grafting	Total amputations	Died
Anderson *et al.*[34]	1974	Brachial	1	None	0	0	0	0 (0)	0
		Femoral	3	Selective	0	1	1	1 (33)	0
Johnson *et al*[33]	1983	Brachial	8	None	0	0	0	0 (0)	0
		Radial	4	None	0	0	0	0 (0)	0
		Femoral	40	Selective	4	6	2	6 (15)	0
Feldman and Berguer[36]	1983	Femoral	30	Selective	5	6	0	5 (17)	0
		Femoral	23	Compulsory	0	23	4	4 (17)	1
Reddy *et al*[37]	1986	Single femoral vessel	26	Selective	0	0	0	0 (0)	0
		Femoral bifurcation	28	Selective	6	10	0	6 (21)	0
Benitez and Newell[16]	1986	Upper limb	20	None	0	0	0	0 (0)	0
		Lower limb	112	Selective	13	16	3	16 (14)	2
Patel *et al.*[38]	1988	Femoral	1	None	1	0	0	1 (100)	0
		Femoral	15	Compulsory	0	15	1	1 (7)	0
Welch *et al*[39]	1990	Femoral	6	Compulsory	0	8	0	0 (0)	0
Cheng *et al*[35]	1992	Single femoral vessel	8	Selective	0	1	0	0 (0)	0
		Femoral bifurcation	13	Selective	1	1	0	1 (8)	0

Values in parentheses are percentages

Table 3 Complications following revascularization surgery after excision of femoral false aneurysms in drug addicts

Reference	Year	Graft material	Site of graft	No. of cases	Haemorrhage/ occlusion/ infection	Amputation
Johnson *et al*[33]	1983	Vein	Interposition	1	0	0
		Synthetic	Interposition	1	0	0
		Synthetic	Remote	4	3	2
Feldman and Berguer[36]	1983	Vein	Remote	3	8	4
		Synthetic	Remote	20		
Reddy *et al*[37]	1986	Vein	Interposition	6	1	0
		Synthetic	Remote	3	3	0
Patel *et al.*[38]	1988	Synthetic	Interposition	3	1	1
		Synthetic	Remote	12	0	0
Welch *et al*[39]	1990	Vein	Interposition	1	1	0
		Synthetic	Interposition	4	4	0
		Synthetic	Remote	3	0	0
Cheng *et al*[35]	1992	Synthetic	Remote	2	0	0

obturator route[37,38], or the lateral thigh route[36,39] is to be favoured over direct interposition grafting in the groin. Placing a synthetic iliofemoral interposition graft in the groin after excision and ligation of an infected femoral pseudoaneurysm results in graft occlusion, infection and haemorrhage which may be less frequent following remote synthetic grafting (*Table 3*). The results of direct interposition grafting with autogenous vein, if available, may reduce these complications[37] although anastomotic disruption is a likely complication in the early postoperative period following all types of interposition grafting[39]. The most prudent course in the treatment of infected femoral pseudoaneurysm would therefore appear to be one of excision and ligation with selective revascularization using an iliofemoral graft (vein or synthetic) placed at a site remote from the involved groin.

Conclusion

Despite the increase in drug misuse by injection and the wide variety of complications encountered in drug abusers, only a limited number of retrospective reports have addressed the problem of vascular complications. It does, however, appear that the need for specialist vascular surgical referral is more or less limited to infected femoral pseudoaneurysm. This lesion should be suspected in any injecting drug addict with an appropriately sited swelling; it must be identified before surgery if safe and appropriate treatment is to be achieved. The risk of limb loss after operation should be clearly explained to these patients. With the exception of infected venous pseudoaneurysm, which is usually diagnosed at operation to drain an abscess, surgery has little part to play in the management of other vascular complications of drug injection; supportive medical therapy is often all that is required.

Acknowledgements

The authors thank Mr R. N. Scott, Consultant Surgeon, Monklands District General Hospital, Dr J. J. Going, Department of Pathology, Glasgow Royal Infirmary, and

Vascutek Ltd, Inchinnan, UK, for permission to reproduce the illustrations used in this article.

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British Journal of Surgery 1996, 83, 1335–1344

Review

Aetiology and treatment of anal fissure

J. N. LUND and J. H. SCHOLEFIELD

Department of Surgery, University Hospital, Nottingham NG7 2UH, UK
Correspondence to: Mr J. H. Scholefield

Anal fissure is a common problem that causes significant morbidity in a young and otherwise healthy population. Treatment has remained largely unchanged for over 150 years and the pathogenesis of this condition is not yet fully explained. Acute fissures should be treated conservatively with dietary modification. Chronic fissures do not respond to conservative treatment. The current recommended surgical treatment for chronic fissure is lateral internal sphincterotomy. However, there is a disturbance of continence in a sizeable proportion of those undergoing this procedure. As yet there is no proven non-surgical treatment for chronic fissure. Although local injection of botulinum toxin and the topical application of nitrates show early promise, further controlled trials are needed.

A systematic review of the aetiology and treatment of anal fissure has been performed. European language literature between the years 1975 and 1995 was assayed from Medline. Historical articles were identified from citations in these articles.

Anal fissure is a split in the skin of the distal anal canal. It is a common complaint in young adults with a roughly equal incidence in both sexes[1]. Acute fissures are probably very common and most heal spontaneously, but a proportion progress to form a chronic linear ulcer in the anal canal and show great reluctance to heal without intervention. Classic symptoms are pain on or after defaecation which is often severe and which may last from minutes to several hours. Often there is bright blood on the toilet paper. Patients may also complain of pruritus.

The majority of anal fissures occur in the posterior midline of the anal canal but 10 per cent of fissures in women and 1 per cent in men occur in the anterior midline[2]. Multiple fissures or fissures occurring in the lateral position arouse suspicion of other diseases including Crohn's disease, ulcerative colitis, tuberculosis, human immunodeficiency virus or syphilis. However, the majority of fissures seen in patients with inflammatory bowel disease occur in the posterior midline and are painful in at least half of cases[3,4].

The fissure may be seen as the buttocks are parted. Anal fissure is often suspected because there is marked spasm of the anus making examination difficult. Digital or proctoscopic examination is often impossible because of pain experienced by the patient. Under a general anaesthetic the fissure is seen as a linear or pear-shaped breach in the lining of the anal canal below the dentate line. Acute fissures are generally differentiated from chronic fissures by their appearance. Acute fissures are superficial splits in the anoderm with sharply demarcated edges. When the fissure is chronic, induration at the edges of the fissure may be seen and the horizontal fibres of the internal anal sphincter (IAS) may be visible in the base. There is a notable lack of granulation tissue at the base of the fissure. A skin tag may be present distally. Although there is no strict temporal definition of chronicity it is suggested that any patient with persistent symptoms for more than a few weeks will usually have a chronic fissure[2,5].

Physiological and pharmacological control of the internal anal sphincter

The human IAS exists in a state of partial contraction and relaxes in response to rectal distension (the rectosphincteric reflex). Sympathetic innervation from the fifth lumbar segment via the hypogastric nerves is responsible for a proportion of the tonic contraction but there is also a large myogenic component[6,7]. Contraction of isolated strips of human IAS is mediated by α-adrenoceptors. Relaxation is mediated by β-adrenoceptors[8]. The α-adrenoceptor population is dominant as the contractile response to noradrenaline can be converted to relaxation only when selectively blocking α-adrenoceptors[8]. These results are supported by experiments on normal volunteers[6]. Acetylcholine has a predominantly inhibitory effect on isolated IAS tone mediated by muscarinic receptors[8,9].

Electrical field stimulation (EFS) mimics the effect of extrinsic nerve stimulation of isolated smooth muscle strips. Human IAS relaxes in response to EFS. This relaxation is abolished by tetrodotoxin, a universal neurotoxin, indicating that the relaxation is nerve mediated[8]. Relaxation induced by EFS is unaffected by antagonists of acetylcholine and is therefore mediated by a non-adrenergic, non-cholinergic (NANC) neurotransmitter. Adenosine triphosphate and vasoactive intestinal polypeptide have both been suggested as candidates for NANC neurotransmission but their role has not been substantiated in man[8,10]. It seems likely that NANC neurotransmission is mediated by nitric oxide.

In an animal model Rattan and Chakder[11] demonstrated concentration-dependent relaxation of the IAS in response to nitric oxide which was similar to that seen in NANC nerve stimulation by EFS. NANC nerve-mediated IAS relaxation was blocked by inhibition of nitric oxide synthase (NOS) with L-NNA(N^5-(nitroamidino)-L-2,5-diaminopentanoic acid. This blockade was reversed stereoselectively by L-arginine, a substrate for NOS. Nω-nitro-L-arginine, an inhibitor of the L-arginine–nitric oxide pathway, produced a concentration-dependent reduction in opossum IAS relaxation to EFS[12]. Nitric oxide was released following EFS of NANC neurones from isolated muscle strips of opossum IAS using a chemiluminescence method for detecting nitric oxide[13].

Paper accepted 7 June 1996

O'Kelly *et al.*[14] demonstrated the presence of neurones containing NOS in the rectal myenteric plexus which ramified throughout the IAS and lay in close proximity to smooth muscle cells. In Hirschsprung's disease, a condition in which the rectoanal inhibitory reflex is absent, nerves containing NOS were absent from the non-relaxing segment but present in the normal segment of gut[15]. Although nitric oxide release was not demonstrated directly, its involvement in nerve-mediated relaxation was strongly suggested by *in vitro* studies on human IAS[16].

Pathogenesis of anal fissure

Historical perspective

The passage of a hard stool bolus has traditionally been thought to cause anal fissure. Ball[17] suggested that the passage of a hard stool tore down an anal valve leaving the coiled up skin at the anal verge as the sentinel pile. This does not explain why fissures tend to occur in the midline and anal valves can still be seen at the upper end of a fissure. Fibres of the superficial external anal sphincter decussate to form a Y shape posteriorly; the overlying skin was said to be poorly supported and was prone to tear on passage of a large stool[18]. However, a history of constipation preceding the onset of anal fissure is obtained only in one of four cases and diarrhoea is seen to be a predisposing factor in 4–7 per cent of patients[5 19 20].

Varicose veins of the anal canal have been implicated in the formation and persistence of anal fissure; Miles[21] suggested that these varicosities were the result of a 'pecten band' in the distal anal canal and that the fissure persisted because of phlebitis of these vessels. Division of this 'pecten band' was advised as treatment. It was later shown by Eisenhammer[22] that this band was in fact the hypertonic IAS.

Anal fissure may be associated with childbirth in between 3 and 11 per cent of patients and commonly occurs in the anterior midline[5 23 24]. Shearing forces from the foetal head on the anal mucosa or mucosal tethering after childbirth rendering it more susceptible to trauma have both been incriminated but are difficult to substantiate.

Spasm of the anal sphincter has been noted for many years in association with anal fissure and surgical treatment has generally been aimed at overcoming this spasm[25]. Brown and colleagues[26] found that the IAS of patients with anal fissure was fibrotic compared with that of controls. It was postulated that a myositis occurs early in the course of a fissure and that this is the underlying cause of both spasm and fibrosis. However, the cause of the spasm remains obscure.

Early reports[27–29] failed to demonstrate raised anal pressure in small groups of patients with anal fissure. However, the majority of studies have consistently found resting anal pressure to be significantly higher in patients with anal fissure than in normal controls using a variety of techniques[30–43]. Maximum voluntary squeeze pressure in patients with fissure is no different from that in controls, suggesting that the high resting pressure is due to hypertonicity of the IAS. Application of local anaesthetic to the fissure has no effect on resting anal pressure[41]. Also, resting anal pressure in patients healed by conservative treatment tends to increase to pretreatment level while the patient remains symptom free[44]. Both of these observations suggest that the spasm of the IAS is not secondary to local pain. An abnormal anorectal inhibitory reflex and a longer high-pressure zone has been noted in patients with chronic anal fissure but is not a consistent finding[28,30,32,39,45,46]. Ultraslow pressure wave activity occurs more frequently in those with chronic anal fissure than in controls[33,39]. This activity is abolished after sphincterotomy.

Current theories

The blood supply of the distal anal canal is via the inferior rectal arteries, branches of the internal pudendal artery. These vessels cross the ischiorectal fossae and divisions pass through the anal sphincters to reach the mucosa. Post-mortem angiography of the inferior rectal artery was performed in 41 subjects by Klosterhalfen *et al.*[47]. Two variants of the inferior rectal artery were demonstrated. In the first, a paucity of branches of the inferior rectal artery was seen at the posterior commissure. This variant was noted in 85 per cent of cases. In the second, the inferior rectal artery supplied branches to the posterior commissure as well as to other parts of the distal anal canal. Morphometric study of the capillaries revealed them to be less dense in both the subanodermal space and within the IAS in the posterior midline in the majority of subjects. It was suggested that ischaemia of the posterior midline may explain the predilection of anal fissures for this position and the lack of granulation tissue seen in the base of a chronic anal fissure.

Raised pressure of the IAS associated with anal fissure reduces the perfusion pressure of the mucocutaneous lining to levels equivalent to a perfusion index of 0·29, which may produce rest pain and ulceration when seen in the lower limb[36]. Internal anal sphincterotomy or anal dilatation, which lower the pressure exerted by the IAS, may restore normal perfusion of the anoderm leading to relief of pain and healing of the fissure. Schouten and colleagues[48] demonstrated reduced blood flow at the posterior commissure of the anal canal compared with that in the other three quadrants using laser Doppler flowmetry. Anodermal blood flow was negatively correlated with resting anal pressure. When resting anal pressure fell under anaesthesia, a rise in anodermal blood flow was noted. After lateral sphincterotomy a significant fall in resting anal pressure and a significant rise in anodermal blood flow was observed to levels seen in controls[49]. It seems that ischaemia may play an important part in the pathogenesis of chronic anal fissure.

Treatment of anal fissure

Non-surgical

Since the passage of a hard stool has been thought to contribute to the development of anal fissure the avoidance of constipation has been used as treatment for many years[50 51]. In a prospective case–control study, a diet that contained raw fruit, vegetables and wholegrain bread significantly decreased the risk of developing anal fissure. Significantly increased risk of developing a fissure was noted in those who frequently consumed white bread, sauces thickened with roux, and bacon or sausages[52]. In treatment of acute anal fissure, dietary bran supplements and warm sitz baths were shown to be superior to topically applied local anaesthetic or hydrocortisone cream, healing 87 per cent after 3 weeks[53]. Recurrence of acute fissure was also significantly decreased when 5 g unprocessed bran was taken three times daily compared with that after placebo (lactulose) and 2·5 g bran[54]. There are no trials examining the effect of diet on the course of chronic anal fissure. Following local anaesthetic treatment[55] of pruritus ani, Gabriel[56] and Morgan[57] treated a mixture of acute and chronic fissures by injection of local anaesthetic solutions into the sphincter on either side of the fissure[55–57]. Healing was seen in less than half of the patients and many complained of severe pain following injection lasting for several hours. Injection was often complicated by local sepsis and temporary incontinence, and was largely abandoned[2,58]. Local injection of sclerosant was also complicated by sepsis and many patients suffered early relapse[59].

Avoiding operation by means of applying a pharmacological preparation locally has been attempted since the early 19th century when belladonna suppositories were used but were later abandoned because of systemic side-effects[25,60]. There are presently over a dozen proprietary preparations available in the UK which may be applied topically to alleviate the symptoms of anal fissure. Preparations contain soothing agents, such as bismuth subgallate or zinc oxide, often in combination with local anaesthetics or topical steroids. The majority of these preparations have not been evaluated in scientific trials.

Dietary supplements of unprocessed bran, topical lignocaine 2 per cent gel or topical hydrocortisone 2 per cent ointment were compared in a prospective randomized trial in patients with acute fissure[53]. No difference was seen in symptomatic relief between groups but significantly fewer fissures healed in patients treated with local anaesthetic (60 per cent) than in the other two groups (82–87 per cent). One patient treated with hydrocortisone developed extensive previously undiagnosed anal herpes. The use of local anaesthetic agents may occasionally lead to sensitization of the skin[61]. Two other studies[19,20] using lignocaine gel in the treatment of acute fissure found that half of the patients were referred for surgery and that, of those initially cured, half would eventually relapse. It was suggested that the presence of a skin tag or fibrous anal polyp were significant predictors of failure to respond to conservative treatment and that local anaesthetic treatment be reserved for acute fissure. However, healing was observed in 45 per cent of patients with symptoms of over 6 months' duration when treated with lignocaine gel; over half of these patients had sentinel tags[24].

Anal dilators have been employed in the treatment of anal fissure for many years[25,62]. They were popular for some time but have been criticized as being merely a reliable way of applying an anaesthetic ointment[2,20]. It was recommended that the instrument, usually a St Mark's dilator of medium size, be coated in anaesthetic jelly and inserted into the anal canal before the passage of stool to prevent exacerbation of symptoms during defaecation, and at two or three other times during the day[20]. Two small studies[58,63] reported that more than half of the patients were initially cured using this technique but that half of those cured would relapse; a larger retrospective study at St Mark's Hospital, London, confirmed these results[20]. The majority of those who were cured initially had acute fissure. Conservative treatment was found to be inferior to lateral internal sphincterotomy in 308 patients with acute and chronic fissures[44]. Later prospective randomized trials, comparing the use of an anal dilator plus anaesthetic jelly with digitally applied anaesthetic jelly alone reported no difference between the two groups for acute fissure[19] or chronic posterior fissure[24]. Overall, almost half of the patients in each group were referred for surgery, although a retrospective analysis of patients with anterior fissure suggested that this fissure may respond better to conservative therapy[24].

A combination proprietary ointment Proctosedyl (Roussel Laboratories, Uxbridge, UK), containing cinchocaine hydrochloride and hydrocortisone, was used in the treatment of acute fissure with an overall healing rate of 80 per cent[64]. This trial was uncontrolled and involved 133 patients including infants, children and adults seen in 45 general practices across the country. Those patients in whom constipation was relieved had a better outcome.

Local anaesthetic has been combined with a proteolytic enzyme derived from mammalian pancreas or papaya in the treatment of acute fissure[65]. In this small uncontrolled study, healing was noted in all patients but all also had stool softener and sitz baths. There was no follow-up after initial healing. Other preparations that are said to promote healing in tissues when applied locally have been investigated in the treatment of acute fissure[66–69], but have not gained widespread acceptance.

Surgical

Récamier[70] in 1838 is widely cited as giving the first description of anal stretch. Since this time its popularity for treatment of anal fissure has waxed and waned. Its use was recommended by Goodsall[51] at the turn of the century and later by Gabriel[56] and others[2,29,71]. Surgeons have been attracted to the procedure by 'its extreme simplicity' and because 'it can be easily performed by relatively junior staff without any special equipment'[2,29]. However, the technique is difficult to standardize and is criticized for causing uncontrolled tearing of the sphincter[72].

The amount of force used, degree and duration of stretch recommended varies between authors, but many have used four fingers inserted into the anal canal for at least 4 min[2,29,50,71,73,74]. Responding to criticism of the imprecise nature of anal dilatation some authors have attempted to standardize the procedure with lengths of string around the fingers limiting distraction, or replacing fingers with a Parks retractor or a balloon so that overstretching and tearing of the sphincters does not occur[73,74]. Comparison of the results of anal dilatation is difficult as there is no standard technique and follow-up differs between trials. It seems likely that problems will present with longer follow-up or if the patient is asked about difficulty controlling flatus or soiling of the underclothes rather than incontinence[75]. Patients with acute and chronic fissures often are included in the same treatment group, making healing rates difficult to interpret. Of 16 trials[29,58,71,74–86] examining the use of anal dilatation in the treatment of anal fissure, most reported rapid and effective symptomatic relief following the procedure. Recurrence of the fissure was reported as 2·2–56·5 per cent and tended to be higher with longer follow-up. Disturbance of continence ranged from 0 to 39·2 per cent for incontinence of flatus or soiling of the underclothes, and faecal incontinence was reported in up to 16·2 per cent. Four-finger dilatation was used in ten of these trials; there was widely varying outcome in both the incidence of recurrence and incontinence, highlighting the interoperator variation in performing the procedure as much as the differences in data collection.

Patients who complain of impairment of continence following anal dilatation have low resting anal pressures and low voluntary squeeze pressures[87,88]. Of 12 men who had faecal incontinence subsequent to anal dilatation, 11 were noted to have disruption of the IAS using anal endosonography[87]. Fragmentation of the IAS was seen, rather than a single tear, with disruption of a mean of 153° of the sphincter circumference. In some, the remaining sphincter showed signs of degeneration and an increase of connective tissue. Three of the patients studied also had defects of the external anal sphincter. Nielsen and co-workers[89] performed anal endosonography on 20 consecutive patients 2–6 years after anal dilatation. Two of the study group complained of minor disturbance of continence; both had defects in the IAS. However, 11 of the 18 continent patients had sphincteric defects, four of whom had fragmentation of the IAS. Although these patients did not complain of incontinence they may be at risk if the sphincter weakens with age or further anal surgery is performed[72].

Anal dilatation may also be complicated by bleeding from the fissure requiring later admission, perianal bruising, strangulation of associated prolapsed haemorrhoids, perianal infection, Fournier's gangrene and full-thickness rectal prolapse in elderly women[29,71,74,79,82–84,90,91]. Bacteraemia was noted in 8 per cent of patients having anal dilatation and the use of prophylactic antibiotics in those who are immunosuppressed or have cardiac valve disease or prosthetic valves is advocated[92].

Operations involving the incision of sphincter muscle around the anus have been performed since the early 19th century[25,60]. Until Eisenhammer[22] clarified the anatomy of the anal canal it was believed that these operations divided a part of the external sphincter, when in all probability the IAS was divided[93]. Since this time internal anal sphincterotomy has become one of the most frequently performed surgical procedures with many variations in technique described. Division of the internal sphincter through the base of the fissure in the posterior midline, with or without fissurectomy, was employed for many years[60,94]. However, the sphincterotomy wound is slow to heal in comparison to the wound after lateral spincterotomy and hospital stay is longer[78,95]. Immediate skin grafting of the sphincterotomy wound in an effort to speed healing has not found general acceptance[96]. High rates of soiling of the underclothes after the procedure have been reported[1,78,95,97]. On inspection of the anus a gutter in the posterior midline was seen in up to 28 per cent of patients after midline sphincterotomy. This 'keyhole deformity' caused imperfect closure of the anal canal or trapping of faecal residue which later discharged on to the underclothes. Some authors report that this complication is not observed when the deeper fibres of the IAS are not divided and Mazier[100] believed that there was little problem with keyhole deformity after posterior sphincterotomy[98–100]. However, Mazier's study group consisted of patients presenting with incontinence of any cause and he did not follow up patients after posterior sphincterotomy.

Randomized prospective trials of posterior *versus* lateral sphincterotomy favour the latter[78,95], which was described by Brodie in 1835[25]. Brodie recommended lateral rather than posterior sphincterotomy because of the shorter healing time of the former. Lateral sphincterotomy is now the treatment of choice in anal fissure for many surgeons[101]; it may be performed using an open or a subcutaneous technique and under local or general anaesthesia[102,103]. Both open and subcutaneous methods produce adequate and equivalent falls in anal pressure[104]. One prospective trial comparing the two methods found that hospital stay and pain after operation were less after closed sphincterotomy, although less than half of the patients completed the pain questionnaire[105]. A larger prospective trial[106] found no difference between the two methods in terms of recurrence rate, postoperative complications or short- and long-term impairment of continence. Another recent retrospective study[107] followed up patients who had open or subcutaneous sphincterotomy by questionnaire and found that, while there was no difference in recurrence rate or the need for reoperation between the two procedures, there was more soiling and faecal incontinence in those undergoing open sphincterotomy.

The results of lateral sphincterotomy have been reported from many centres (*Table 1*). Complication rates vary, but the largest studies report impairment of continence in up to 30 per cent of patients. These are reports of results from largely unselected series of patients, although none include reoperation for recurrent fissure. Only one study measured resting anal pressure before operation, but no patients were excluded because of low pressure[104]. Although incising the whole length of the IAS is inadvisable, it is uncertain just how much of the sphincter should be divided; a consensus view appears to be to divide the sphincter for the length of the fissure. It has been suggested that the incidence of recurrence and alteration of continence is not affected by length of the sphincterotomy[1]. However, a prospective study[121] of the extent of IAS division at sphincterotomy using anal endosonography suggested that more of the IAS than intended was divided, especially in female patients. A further endosonographic study[122] examining patients with persistent anal fissure after lateral internal sphincterotomy found that in five of seven patients no defect could be detected in the IAS, although defects in the external anal sphincter were observed at a site consistent with the position of the previous sphincterotomy. The American Society of Colon and Rectal Surgeons[101] recommend caution before performing internal sphincterotomy in patients with diarrhoea, irritable bowel syndrome and diabetes, and in the elderly. In view of the above reports, the authors recommend that before further surgery for fissure is contemplated, resting anal pressure should be recorded and the anal sphincter complex visualized by endoanal ultrasonography in those patients with recurrent fissure after previous surgery, and in women who have previously undergone episiotomy or suffered a third-degree tear during labour.

Sphincterotomy may be performed under local or general anaesthesia. Despite reports of higher recurrence rates after procedures performed under local anaesthesia, several authors advocate performing sphincterotomy as an outpatient procedure and describe good results[111,112,117,123].

Several comparisons of internal sphincterotomy with anal dilatation in the treatment of anal fissure have been made. Two studies on successive consecutive groups of patients were reported from Leeds, the first group treated by sphincterotomy[1], the second by anal dilatation[71]. Recurrence of the fissure was seen twice as often after dilatation than after sphincterotomy; however, minor defects of continence were observed more frequently after sphincterotomy. Goligher[2] subsequently recommended anal dilatation as initial treatment for fissure with

Table 1 Results of lateral sphincterotomy for anal fissure

Reference	Year	No. of patients	Technique	Incidence of incontinence (%)	Complications (no. of patients)	Length of follow-up	Recurrent/unhealed fissures (%)	Median time to healing
Hawley[78]	1969	24	Open and closed; IAS divided to dentate line	0	—	—	0	3·5 weeks
Hoffmann and Goligher[108]	1970	99	Closed; IAS divided to dentate line	Flatus 6 Soiling 7 Faeces 1	Bleeding 1 Abscess 1 Bruising 22 Prolapsed haemorrhoids 2	3–24 months	3	4 weeks
Notaras[109]	1971	82	Closed; IAS divided to dentate line	Flatus 2·4 Soiling 4·8 Faeces 1·2	Prolapsed haemorrhoid 1	6 months	0	3 weeks
Ray *et al* [110]	1974	21	Open; IAS divided to dentate line	—	Cellulitis 1	—	—	3 weeks
Rudd[111]	1975	200	Open, length of fissure	0	0	3–24 months questionnaire (111 patients only)	1	2 weeks
Bailey *et al* [112]	1978	418	Open; IAS cut to allow admission of large Ferguson–Hill retractor	Flatus 1·2 Faeces 1·2	Abscess 3 Bleeding 4 Fistula 5 Retention of urine 1	—	1	< 6 weeks
Oh[113]	1978	300	Closed and open	Flatus 1 Soiling 2 Faeces 0·6	Bleeding 8 Infection 4 Fistula 1	—	0·5	—
Abcarian[95]	1980	150	Open; distal half of IAS divided	Flatus 30	Fistula 1 Abscess 1	—	1 3	—
Milito *et al.*[114]	1983	117	Open; lower two-thirds of IAS divided	Flatus 32 5 Soiling 3·4	—	12 months	0	4 weeks
Hsu and MacKeigan[115]	1984	89	Open; lower third of IAS divided	—	Abscess 1	—	5·6	—
Boulos and Araujo[104]	1984	24	Open; IAS divided to dentate line	Flatus 20	Infection 2 Bruising 9	—	0	—
Walker *et al.*[116]	1985	306	Open and closed	Flatus 6·2 Soiling 2	Abscess 7 Bleeding 14 Impaction 3 Pruritus 26	4·3 years	—	—
Gordon and Vasilevsky[117]	1985	133	Open; IAS divided to dentate line	Flatus 2·3 Faeces 0·8	—	12 months	1·5	—
Lewis *et al.*[106]	1988	350	Open and closed; IAS divided to dentate line	Flatus 17 Faeces 0·03	Abscess 8 Bleeding 1	Median 37 months	6	—
Viso Pons *et al* [118]	1989	100	—	0	Pyrexia 5 Bruising 2 Fistula 1 Abscess 1	—	—	—
Khubchandani and Reed[119]	1989	657	Open and closed	Flatus 36 Soiling 21 Faeces 4·9	—	—	2·3	5·6 weeks
Pernikoff *et al.*[120]	1994	500	Open and closed; IAS cut to allow admission of large Ferguson–Hill retractor	Soiling 4·4 Flatus 3 Faeces 0 4	Bleeding 7 Discharge 2 Abscess 1	Median 5·6 years by questionnaire	3	—

IAS, internal anal sphincter

sphincterotomy reserved for recurrence. However, posterior midline sphincterotomy was performed in these patients and many of those found to have impaired continence were seen to have a keyhole deformity of the anus. Later, on changing to lateral sphincterotomy, impairment of continence became less than was observed following dilatation and this method was recommended as the initial treatment of choice[2,108]. Retrospective follow-up by questionnaire in another group of patients found that recurrence of pain and problems of incontinence were seen less often after lateral sphincterotomy[82].

A prospective randomized controlled trial comparing the two methods was performed in 66 patients by Fischer and Hamelmann[85]. After 2 years of follow-up the incidence of incontinence was significantly greater after dilatation. No statistical difference in the recurrence rate was observed. Further prospective randomized trials have demonstrated a lower recurrence rate and fewer complications following lateral sphincterotomy[79,83,86]. Two other prospective randomized controlled trials have not shown any difference between the two methods[80,81]. Marby *et al.*[84] reported that improvement was seen in 93 per cent of patients by 4 months after anal dilatation compared with 78 per cent after lateral sphincterotomy, and that recurrence was seen in significantly fewer patients randomized to dilatation. However, in this trial sphincterotomy was performed under local anaesthetic and anal dilatation under general anaesthetic. The same group reported later[123] that 53 per cent of fissures recurred after treatment by lateral sphincterotomy under local anaesthetic, compared with only 3 per cent after the same procedure performed under general anaesthesia. It may be that inadequate sphincterotomy was performed under local anaesthesia.

Laser instruments have been used to perform internal sphincterotomy in the place of scissors or a scalpel blade, with no great advantage[124,125]. Advancement flaps have been used to cover the fissure with perianal skin to promote primary healing. A broad based V–Y advancement flap has been used to treat patients who had normal or low resting anal pressure in the presence of anal fissure[126]. Twenty-one patients, the majority having had previous lateral sphincterotomy or obstetric trauma, were treated by V–Y advancement flap with no flap necrosis or disturbance of continence. All fissures healed after treatment by this method. A prospective randomized trial to compare a rhomboid advancement flap with lateral sphincterotomy was performed with 20 patients in each group[127]. All fissures healed after sphincterotomy whereas three of 20 failed to heal after treatment by advancement flap, two of which were subsequently successfully treated by sphincterotomy. Advancement flaps may have a role in the treatment of fissures that occur in the presence of low anal pressure where further division of muscle would be undesirable.

Management of anal fissure in Crohn's disease

The management of fissure associated with Crohn's disease is controversial. In a recent series[4] of patients with fissure associated with Crohn's disease there were complications in 13 of 50 patients who remained unhealed after conservative treatment. Six ultimately required proctectomy for sepsis originating from the site of the fissure. Despite this report, the consensus remains that fissures associated with Crohn's disease should be treated conservatively and surgery reserved for the complications which occur in 10 per cent of cases. These include sepsis and fistula arising from the base of the fissure[2,3,128].

Recent innovations

Botulinum toxin is one of the most lethal of biological toxins; it acts rapidly and strongly binds to presynaptic cholinergic nerve terminals[129]. The toxin is internalized and inhibits calcium-dependent exocytosis of acetylcholine[130]. Paralysis occurs within a few hours. Transmission of neuromuscular impulses resumes after the growth of new axon terminals and clinical weakening of muscle is seen for 3–4 months. Botulinum toxin has been used to weaken striated muscle in the treatment of disorders such as blepharospasm and spasmodic torticollis; it may also weaken smooth muscle in the gastrointestinal tract[129,131–134].

Small uncontrolled trials using botulinum toxin to treat anal fissure have been reported[135–137]. Jost and Schimrigk[135,136] treated 12 patients with chronic anal fissure and increased basal sphincter tone who had not responded to conservative treatment with 0·1 ml diluted botulinum toxin 50 units/ml injected into the external sphincter on either side of the fissure. Eight patients reported that they were free from pain on the first day after injection. Manometry performed on day 5 showed a reduction in maximum voluntary squeeze pressure. At 3 months the fissure was healed in ten of 12 patients. Brief episodes of incontinence have been reported in three of 50 patients so far treated. Five of 26 women have developed perianal thrombosis after injection; this complication has not been noted in men[138].

Gui and colleagues[137] injected botulinum toxin of the same strength as above into three sites in the internal sphincter of ten patients with chronic anal fissure. Pain was absent in five patients and reduced in four at first review at 1 week, and had disappeared at 1 month in seven of ten patients. Resting anal pressure was significantly lowered compared with pretreatment values, while maximum voluntary squeeze pressure was unaffected. Healing was seen in eight patients at 2 months. Two relapsed; one was successfully treated with further botulinum toxin and the other requested surgical sphincterotomy. One patient reported a brief episode of faecal incontinence following treatment.

The site of action of botulinum toxin remains unclear. The fall in resting pressure whilst squeeze pressure remained unchanged after injection into the IAS suggests that the toxin may be acting by weakening the IAS with no effect on the external sphincter[137]. However, injection of toxin into the external anal sphincter leads to similar healing rates with a reduction in maximum squeeze pressure. No mention of the change in resting pressure is made by Jost and Schimrigk. As the external anal sphincter consists of skeletal muscle, it may be postulated that this weakening of the external sphincter occurs via the effect of botulinum toxin on cholinergic neurones. However, acetylcholine has an inhibitory effect on the IAS and blockade of its release by botulinum toxin would be expected to cause an increase in anal tone[8]. Botulinum toxin has also been seen to antagonize responses to noradrenaline but not to affect NANC-mediated responses to EFS in guinea pig ileum; it may be that NANC neurotransmitters act unopposed on the IAS after injection of botulinum toxin[139]. What significance the weakening of the external anal sphincter has in healing chronic anal fissure remains controversial and long-term results are not yet available.

There is strong evidence that nitric oxide plays a major role in mediating the relaxation of the IAS[11,14,16]. Exogenous organic nitrates are degraded by cellular metabolism releasing nitric oxide[140]. Sublingual nitroglycerin spray was found to reduce the resting anal pressure for a short period of time but with unacceptable side-effects[141]. Guillemot and co-workers[142,143] reported that topical nitroglycerin ointment rapidly reduced the resting pressure in the upper anal canal in normal subjects and patients with constipation. Basal pressures did not return for a mean of 50 min but a wide variation in the duration of action of the nitroglycerin was observed between patients. No effect on anal resting pressure was observed using a placebo, although the trial was not blinded. Loder *et al.*[144] applied glyceryl trinitrate (GTN) 0·2 per cent ointment to the anoderm of ten patients presenting for physiological assessment of a variety of anal disorders including one with anal fissure. A significant decrease in maximum anal resting pressure was observed by 20 min after application of the ointment which was sustained for at least 9 h after application. These results were confirmed in a small placebo-controlled trial involving patients with constipation, soiling or haemorrhoids.

Topical nitrates have been used in the treatment of acute and chronic anal fissure as well as thrombosed external haemorrhoids[145–148] Eighty-three per cent of acute fissures were healed after 2 weeks of treatment with nitroglycerin 0·3 per cent ointment in a small pilot study, although a high-fibre diet, supplements of phyllium seed and sitz baths were also used[147]. Later results from the same centre reported only nine of 30 patients with acute fissure healed after 2 weeks' treatment on the above regimen, but 23 of 30 by 8 weeks[147]. In both studies a significant reduction in pain, as assessed by linear analogue pain score, was observed within 5 min of application of the ointment and after defaecation. Sixteen patients with chronic anal fissure were treated with isosorbide-dinitrate (ISDN) 1 per cent applied five to six times daily[145]. A significant fall in maximal anal resting pressure was observed within 5 min of application of ISDN; this was sustained for a median of 39 min. Blood flow to the anoderm was assessed using laser Doppler flowmetry and showed a significant and sustained increase compared with pretreatment values. Anal pain was abolished in all patients after 10 days of treatment. Chronic fissures were healed in nine patients after 6 weeks of treatment and in 15 of 16 after 12 weeks. Topical GTN ointment applied twice daily cured 18 of 21 patients with chronic anal fissure after 6 weeks[149]. Previous surgery for anal fissure had been performed in three of the study group, all of whose fissures healed and who therefore avoided further surgery. Little or no fall in maximal anal resting pressure after the application of GTN was observed in patients whose fissure did not heal, including one patient with Crohn's disease.

Many experience mild transient headache when using topical nitrate preparations and an anal burning sensation has also been reported; however, there has been no report of incontinence during treatment[143,145,147]. It has been suggested that those with chronic anal fissure may have a reduced sensitivity to topical GTN ointment and that tachyphylaxis may develop, but this has not yet proved to be a problem in practice[150].

Prospective, placebo-controlled trials and long-term follow-up to assess the recurrence rate of fissures are now needed to evaluate further this method of treatment; this new non-surgical therapy for anal fissure seems promising.

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Association of Surgeons of Great Britain and Ireland

The Annual Scientific Meeting of the Association of Surgeons of Great Britain and Ireland was held in Glasgow on 22–24 May 1996 under the Presidency of Professor Sir Miles Irving. The abstracts of the oral and poster presentations of the original work presented at the meeting were published (a new venture) in a BJS Supplement which accompanied the June 1996 issue of the Journal. A record number of manuscripts of full papers describing work presented in Glasgow have been received by the Journal, and the Editors are pleased to report that the 28 accepted articles that follow also represent a record total.

John Murie
Joint Editor

British Journal of Surgery 1996, 83, 1345–1349

Intestinal barrier dysfunction in clinical and experimental obstructive jaundice and its reversal by internal biliary drainage

R. W. PARKS, W. D. B. CLEMENTS, M. G. SMYE*, C. POPE, B. J. ROWLANDS and T. DIAMOND

*Departments of Surgery and *Clinical Biochemistry, The Queen's University of Belfast, UK*
Correspondence to: Mr R W Parks, Department of Surgery, Institute of Clinical Science, Grosvenor Road, Belfast BT12 6BJ, UK

Intestinal mucosal barrier function in obstructive jaundice was assessed in an animal model and in patients. The effect of internal biliary drainage in patients was also examined. Bile duct ligation for 1 week in the rat resulted in significant bacterial translocation (in seven of 12 animals following ligation *versus* none of the sham-operated controls, $P<0{\cdot}01$). Intestinal permeability, measured by the urinary recovery of orally administered polyethylene glycol, was also significantly increased (+66·2 per cent for ligation *versus* −11·6 per cent for sham, $P<0{\cdot}01$). A prospective study was performed on 33 patients with obstructive jaundice undergoing internal biliary drainage, and results were compared with those in six non-jaundiced patients undergoing laparotomy or endoscopic retrograde cholangiopancreatography and in 11 healthy volunteers. The lactulose : mannitol ratio was used as an intestinal permeability index. Mean(s.e.m.) intestinal permeability assessed before operation was significantly increased in jaundiced patients compared with control patients (0·050(0·010) *versus* 0·016(0·003), $P<0{\cdot}005$). The mean(s.e.m.) lactulose : mannitol ratio in the healthy volunteers was 0·020(0·003), which was similar to that in control patients. In the jaundiced group of patients the intestinal permeability index fell to within normal levels after 28 days of internal biliary drainage (0·050 before operation *versus* 0·021 at 28 days, $P<0{\cdot}02$). These data indicate that intestinal barrier function is impaired in obstructive jaundice and that this impairment is reversed by return of bile to the gastrointestinal tract.

Jaundiced patients undergoing invasive diagnostic and therapeutic procedures are prone to septic complications and renal impairment[1–4], which contribute to postoperative mortality rates varying from 9 to 27 per cent[5,6]. The pathophysiological mechanisms responsible are not fully understood but increased permeation of intestinal bacteria and endotoxins into the portal circulation and impaired Kupffer cell phagocytic function are implicated in the development of these problems[7,8]. In 1959 Fine *et al.*[9] introduced the concept of gut-origin sepsis, in which it was hypothesized that intestinal barrier dysfunction results in the passage of bacteria and their toxins from the lumen to normally sterile extraintestinal sites. This process has been termed bacterial translocation[10] and is demonstrated by culturing bacteria from the mesenteric lymph node complex, liver, spleen or blood in animal models, or from a mesenteric lymph node, serosal scraping or blood in humans.

Bacterial translocation thus provides a method of assessing intestinal barrier function. A significantly higher incidence of septic complications has been described in patients who had bacterial translocation at the time of laparotomy compared with that in those who did not (28 *versus* 11 per cent)[11]. Another method for assessing the integrity of the mucosal barrier, and thus a test of intestinal barrier function, is to measure intestinal permeability. Increased permeability implies functional impairment of the intestinal mucosal barrier and has been shown in burned patients to be a significant risk factor for the development of sepsis[12,13].

The aim of these studies was to investigate the concept of gut-origin sepsis in obstructive jaundice by measuring intestinal barrier function, using the above methods, in an animal model and in patients. In addition, the effect of internal biliary drainage on intestinal permeability was assessed in the clinical setting.

Patients and methods

Animal study

Adult female Wistar rats (250–300 g) underwent common bile duct ligation and division ($n=12$) or sham operation ($n=12$) by means of techniques described previously[14]. The incidence of bacterial translocation and changes in intestinal permeability 1 week after these procedures was determined.

Bacterial translocation

Portal blood culture. Portal blood samples (3 ml) were cultured aerobically and anaerobically with the BacT/Alert

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Paper accepted 4 July 1996

(Oreganon Tecknika, Durham, North Carolina, USA). Blood cultures were monitored continuously for 7 days. Positive blood cultures were plated out on appropriate media and species identified by standard bacteriological techniques.

Homogenization of organs. The mesenteric lymph node complex, spleen and right lobe of liver were removed and placed in preweighed sterile glass bottles containing sterile prereduced brain–heart infusion (BHI). The bottles were reweighed and tissue homogenates prepared in 2 ml BHI with sterile mortars and pestles.

Quantitative and qualitative culture. Aliquots (0·1 ml) of each of the homogenates were cultured on blood agar, chocolate agar, McConkey agar, prereduced tryptone soya agar and blood agar containing neomycin 75 μg/ml. Plates containing the latter two media were placed in an anaerobic cabinet. A further 0·2-ml aliquot was placed in cooked meat broth and plated out on the standard agar plates the following day. All plates were incubated at 37°C. After the appropriate incubation periods, individual colonies were identified and quantified as colony-forming units (c.f.u.) per gram of tissue using the formula:

$$\text{c.f.u. per g tissue} = N \times D \times 2 \times 10/W$$

where N is the number of colonies on the plate, D is the dilution inoculated on the plate, W the weight of the specimen in grams, 2 for the 2-ml BHI, and 10 for the 0·1-ml inoculum.

Intestinal permeability

Intestinal permeability was measured by calculating the percentage change in the 24-h urinary recovery of orally administered radiolabelled polyethylene glycol 4000 ([^{14}C] PEG 4000) given 1 week before and 1 week after operation. PEG 4000 was used as it is a macromolecule whose size mimics that of antigenic substances, such as endotoxin. Radiolabelled PEG solution (1·0 ml) containing 0·142 g PEG per ml (BDH Chemicals, Poole, UK) and 1·1 μCi/ml of [^{14}C]PEG 4000 (Amersham International, Little Chaffont, UK) was administered to each animal by gavage tube[15] The animals were then placed in metabolic cages and the urine was collected for 24 h. Aliquots (0·5 ml) of the collected urine were placed in scintillation vials and 2·5 ml emulsifying scintillation fluid (Aquasafe 300 Plus; Zinsser Analytic, Maidenhead, UK) was added. The vials were placed in a scintillation counter and counts obtained for each vial. The amount of radiolabelled PEG excreted in 24 h was calculated and expressed as a percentage of the total administered dose. Each animal acted as its own control and the percentage change in intestinal permeability from the preoperative value to 1 week after operation was subsequently determined.

Clinical study

A prospective study was performed on 33 consecutive patients with obstructive jaundice (bilirubin concentration greater than 100 μmol/l) undergoing internal biliary drainage as a definitive therapeutic procedure by surgical ($n = 9$), endoscopic ($n = 11$) or percutaneous ($n = 13$) means. The aetiology of the biliary obstruction is shown in *Table 1*. Of patients who had surgical intervention, six had choledocholithiasis and underwent open cholecystectomy with exploration of the common bile duct and three had malignant biliary obstruction. Of the latter group, one had a Whipple procedure and two had biliary bypass procedures performed without resection. Six non-jaundiced patients undergoing laparotomy ($n = 5$) or diagnostic endoscopic retrograde cholangiopancreatography (ERCP) ($n = 1$) and 11 healthy volunteers were also studied. All patients received 1·5 g cefuroxime immediately before the intervention. Systemic or oral antibiotics were not administered routinely following intervention, but were administered if clinically indicated. Each patient was studied on the day before therapeutic intervention and on days 1, 7 and 28 afterwards. Routine liver function tests were performed and intestinal permeability was measured.

Table 1 Aetiology of obstructive jaundice

	Surgery ($n = 9$)	PTC ($n = 11$)	ERCP ($n = 13$)
Choledocholithiasis	6		7
Pancreatic carcinoma	2	5	2
Cholangiocarcinoma	1	6	2
Secondaries in porta hepatis		1	
Sclerosing cholangitis		1	

PTC, percutaneous transhepatic cholangiography; ERCP, endoscopic retrograde cholangiopancreatography

Intestinal permeability

Intestinal permeability was assessed by measuring the urinary excretion of orally administered lactulose and mannitol. This dual sugar absorption test eliminates the effect of variables, such as gastric emptying, intestinal transit, intestinal dilution, bacterial degradation and renal function, as each of the test molecules acts as an internal marker for the other and therefore provides a specific index of intestinal permeability[16,17]. Although the exact pathways used by the probes is still under debate[18], it is thought that mannitol is absorbed transcellularly via the aqueous pores in the cell membrane and is dependent on total absorptive surface area, whereas lactulose is absorbed paracellularly, via the tight junctions and extrusion zones at the villus tips[17]. An increase in lactulose absorption therefore reflects increased intestinal 'leakiness' and intestinal barrier dysfunction, resulting in a raised lactulose : mannitol ratio. After an 8-h fast, the test solution (10 g lactulose and 5 g mannitol dissolved in 50 ml distilled water) was taken orally. Before administration, the bladder was emptied and a pretest sample of urine taken. Subsequently, all urine was collected for a 6-h period. The volume of urine collected was measured and aliquots of this and the pretest sample were stored at − 20°C until assayed. The concentrations of lactulose and mannitol were measured enzymatically by reduced nicotinamide adenine dinucleotide (phosphate)-linked enzymatic assays, modified from techniques described by Northrop *et al.*[19] and Lunn *et al.*[20] respectively, using a Cobras Fara centrifugal analyser (Roche Diagnostics, Welwyn Garden City, UK). Interference from glucose in the lactulose assay was overcome by incubating the sample with glucose oxidase and catalase for 3 h at 37°C before lactulose analysis[21]. Excretion of both substances was corrected by subtraction of baseline values determined on the pretest samples The amount of lactulose and mannitol excreted was calculated as a percentage of the administered dose and intestinal permeability was expressed as the lactulose : mannitol ratio

Statistical analysis

Non-parametric statistical analysis was employed throughout and significance accepted at the 5 per cent level.

Results

Animal study

Significantly raised bilirubin levels were present in rats 1 week after bile duct ligation compared with those in sham-operated controls (258·4 *versus* 5·8 μmol/l; $P < 0·0001$, Mann–Whitney U test).

Bacterial translocation was demonstrated in seven of the 12 jaundiced rats compared with none of the sham-operated animals ($P < 0·01$, Fisher's exact test). In all seven cases in which translocation occurred, *Escherichia coli* was cultured from the mesenteric lymph nodes. In addition, one animal also had Gram-positive bacilli cultured from the mesenteric lymph nodes.

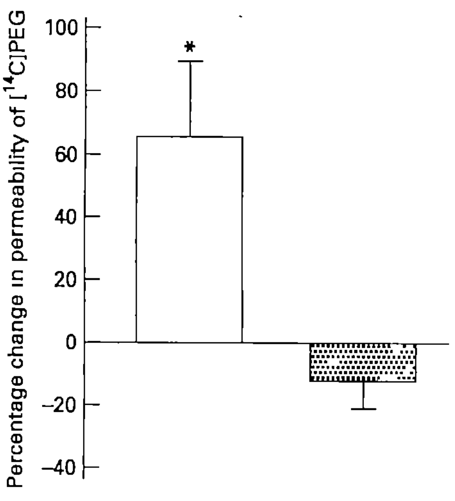

Fig. 1 Mean(s.e.m.) percentage change in intestinal permeability to radiolabelled polyethylene glycol ([^{14}C]PEG) 1 week after bile duct ligation (☐) or sham operation (☐). *$P<0{\cdot}01$ (ligation *versus* sham, Mann–Whitney U test)

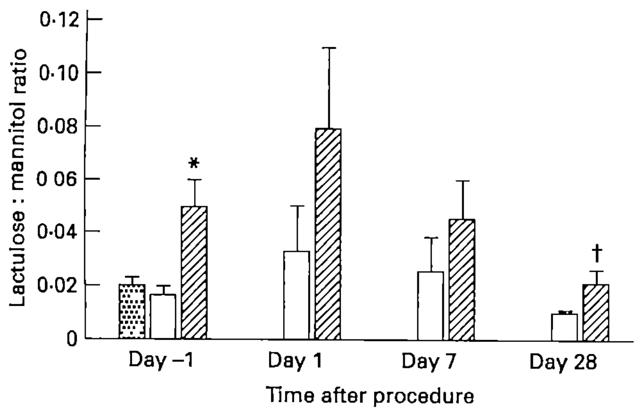

Fig. 2 Means(s.e.m.) lactulose mannitol ratio in jaundiced (▨) and non-jaundiced (☐) patients before and after intervention. ☐, Volunteers. *$P<0{\cdot}005$ *versus* control patients (Mann–Whitney U test); †$P<0{\cdot}02$ *versus* day −1 (Wilcoxon signed rank test)

There was a significant increase in mean intestinal permeability in bile duct-ligated animals compared with sham-operated controls (+66·2 *versus* −11·6 per cent; $P<0{\cdot}01$, Mann–Whitney U test) (*Fig. 1*). There was no significant difference in the percentage change in intestinal permeability between animals demonstrating bacterial translocation and those that did not ($P=0{\cdot}53$, Mann–Whitney U test).

Clinical study

The mean serum bilirubin concentration in jaundiced patients before therapeutic intervention was significantly higher than in control patients (250·2 *versus* 9·7 μmol/l; $P<0{\cdot}0001$, Mann–Whitney U test). After therapeutic intervention the mean serum bilirubin level in jaundiced patients was progressively lower at each of the time points studied, and by day 28 postprocedure fell to within the normal range (156·4 μmol/l on day 1 *versus* 66·9 μmol/l on day 7 *versus* 17·3 μmol/l on day 28).

The mean(s.e.m.) lactulose : mannitol permeability index in 11 normal healthy volunteers (0·020(0·003)) was not significantly different from that in the control group of patients (0·016(0·003)). However, the mean(s.e.m.) lactulose : mannitol ratio for patients with unrelieved obstructive jaundice (0·050(0·010)) was significantly higher than that of control patients studied before operation ($P<0{\cdot}005$, Mann–Whitney U test). There was no significant difference in the mean intestinal permeability index between the subgroups of jaundiced patients before intervention, but each was significantly higher than that in control patients (surgical 0·093 *versus* ERCP 0·036 *versus* percutaneous transhepatic cholangiography 0·040; $P<0{\cdot}05$, Mann–Whitney U test). The lactulose : mannitol ratio in patients with jaundice returned to normal by day 28 after intervention and was significantly less than on the day before the procedure ($P<0{\cdot}02$, Wilcoxon signed rank test) (*Fig. 2*). When jaundiced patients undergoing surgical relief of obstructive jaundice were compared with those undergoing non-operative biliary decompression, there was a significant difference in the intestinal permeability index immediately after the intervention. The mean(s.e.m.) lactulose : mannitol ratio in the surgical group was significantly higher (0·209(0·120)) on the first postoperative day than in the non-operative group (0·042(0·012)) ($P<0{\cdot}05$, Mann–Whitney U test) (*Fig. 3*).

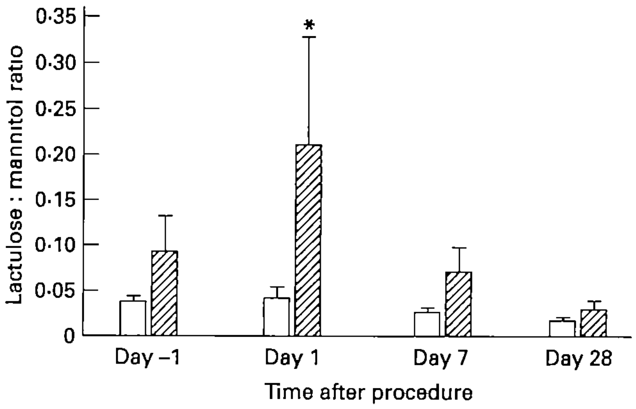

Fig. 3 Mean(s.e.m.) lactulose·mannitol ratio in jaundiced patients before and after surgical (▨) and non-surgical (☐) biliary decompression. *$P<0{\cdot}05$ (surgical *versus* non-surgical, Mann–Whitney U test)

Postprocedural complications occurred in four of the jaundiced patients (acute renal failure in two, urinary tract infection in one, haemorrhage in one). There was no correlation between the occurrence of complications and the initial bilirubin concentration or intestinal permeability index.

Discussion

These studies demonstrate evidence for intestinal barrier dysfunction in obstructive jaundice. Significant bacterial translocation and significantly increased intestinal permeability were demonstrated following experimental biliary obstruction. In addition, significantly increased intestinal permeability was shown in jaundiced patients. Bacterial translocation following bile duct ligation has been reported by others[22–25]. However, the mechanisms by which bacteria escape from the intestinal lumen remain to be clearly defined. Deitch[26] has proposed three factors that promote this process: disruption of the indigenous gut microecology, physical injury of the gut mucosa and impairment of host immunity.

In a previous study, a quantitative and qualitative disruption of the caecal indigenous microflora associated with significant bacterial translocation following bile duct ligation was demonstrated[27]. Bacterial overgrowth and bacterial translocation following experimental biliary obstruction have also been shown by Deitch *et al.*[22] and Ding *et al.*[24]. Deitch and co-workers also described histological evidence of mucosal injury, with subepithelial oedema involving the ileal villi and lifting of the epithelium from the lamina propria. Morphometric evidence of ileal mucosal injury with reduction in villus height and total mucosal thickness in jaundiced rats has been demonstrated[28]. Furthermore, impaired mononuclear cell function has been demonstrated in jaundiced rats[14,29].

To date, there has been limited evaluation of intestinal permeability in experimental models of biliary obstruction or in jaundiced patients[30]. The findings of significantly increased intestinal permeability in the present experimental study were confirmed in the clinical study in which jaundiced patients had a threefold increase in a permeability index compared with non-jaundiced control patients. These data add further support to the hypothesis of intestinal barrier dysfunction in obstructive jaundice.

Returning bile to the gastrointestinal lumen has been assumed to be of benefit and in animal models has reduced postoperative endotoxaemia[31], renal impairment[32] and mortality[33]. Internal biliary drainage has also been considered to be important in the recovery of mononuclear phagocyte function[34,35]. In addition, Ding *et al.*[36] have shown progressively decreased rates of bacterial translocation following choledochoduodenostomy in jaundiced rats, implying an improvement in intestinal barrier function with internal biliary drainage.

In the clinical situation there is conflicting evidence concerning the benefit of internal biliary drainage. In a large study of patients undergoing surgery for pancreatic carcinoma, Trede and Schwall[37] showed that patients who underwent endoscopic internal stenting before surgery had a reduced incidence of postoperative infective complications, and Smith *et al.*[38] demonstrated improved renal function and fewer surgical complications in patients who had a percutaneous stent to allow internal biliary drainage compared with a control group who had immediate surgery. However, Lai *et al.*[39] reported no improvement in postoperative morbidity or mortality in patients who had preoperative endoscopic drainage for malignant obstructive jaundice compared with those who had no preoperative biliary decompression.

In the present study there was an increase in intestinal permeability on the first postoperative day in both jaundiced and non-jaundiced patients. This increase was more marked in patients who underwent surgical intervention than in those who had non-operative biliary decompression, and this may reflect a further endotoxic challenge to intestinal barrier function through exposure to endotoxin at laparotomy[40]. However, by the seventh postoperative day the lactulose : mannitol ratio had returned to preoperative levels. More importantly, in patients with jaundice the intestinal permeability index continued to fall and after 28 days of internal biliary drainage had returned to normal, reflecting a significant improvement in intestinal barrier function with return of bile to the gastrointestinal tract.

In conclusion, this study demonstrates evidence for intestinal barrier dysfunction following experimental biliary obstruction, with significant bacterial translocation and increased intestinal permeability. There was also significantly increased intestinal permeability in jaundiced patients, which returned to normal after 28 days of internal biliary drainage. This suggests that early return of bile to the gastrointestinal tract may improve intestinal barrier function and reduce the incidence of gut-derived sepsis or other complications associated with endotoxaemia in obstructive jaundice.

Acknowledgements

This work was supported by a research fellowship from Charitable Funds of the Royal Victoria Hospital, Belfast, UK.

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British Journal of Surgery 1996, 83, 1350–1355

Influence of different collagenase solvents and timing of their delivery on porcine islet isolation

S. A WHITE, H. H. CONTRACTOR, D. P. HUGHES, P. R. V. JOHNSON,
H. A. CLAYTON, P. R. F. BELL and N. J. M. LONDON

Department of Surgery, PO Box 65, University of Leicester, Leicester LE2 7LX, UK
Correspondence to Dr S. A White

Methods to minimize the effect of cold ischaemia on porcine islet isolation were investigated. Forty pancreata were randomized to intraductal collagenase delivery in University of Wisconsin solution (UW) or Hanks balanced salt solution (HBSS) (control) both before and after 65 min of cold pancreas storage. Collagenase was also administered in a specially designed cold storage solution (University of Leicester solution, ULEIC), before cold storage. Median islet yield was significantly greater if the pancreas was distended with collagenase in either UW (21 524 islet equivalents (IEQ) per g) or ULEIC (19 814 IEQ/g) before cold storage, compared with that after distension with HBSS (6924 IEQ/g) following cold storage ($P < 0.05$). Islet fragmentation, islet purification and glucose-stimulated insulin release were not significantly different after collagenase delivery in either UW or ULEIC compared with those after administration in HBSS. It is concluded that porcine islet yields can be improved significantly by intraductal collagenase administration in either UW or ULEIC immediately after excision of the pancreas.

With the current shortage of human organ donors investigators have been forced to find an alternative source of islet donor tissue[1]. Few would disagree that porcine islets are the most suitable based on their similar physiological and anatomical characteristics to human islets[2]. Nevertheless, porcine islet isolation is extremely variable because of the particular fragility of these cells[3].

Many factors account for the inherent difficulties in the isolation of sufficient numbers of porcine islets from pancreas. One of the problems that needs to be addressed relates to the ischaemic tolerance of porcine pancreas before islet isolation, as all organs removed for transplantation are subject to an inevitable period of both warm and cold ischaemia. In an attempt to circumvent the deleterious effects of warm ischaemia on porcine islet isolation, previous investigators have procured the pancreas from a heartbeating donor as a prerequisite to successful islet isolation[4]. With regard to minimizing the damaging effects of cold ischaemia, a number of different approaches have been used. Application of a cold intravascular perfusate[5] of either EuroCollins solution[6], hyperosmolar citrate (HOC) or University of Wisconsin solution (UW) has proved efficacious in reducing warm ischaemia time, and in combination with hypothermic organ storage has improved cold ischaemic tolerance of human pancreas, before islet isolation[7]. However, when applied to the preservation of porcine pancreas, cold *in situ* vascular perfusion has been shown to culminate in very poor islet yields, mainly because of islet disruption[4].

An alternative and simpler approach to enhance hypothermic pancreas preservation, in the absence of cold *in situ* vascular perfusion, may be to deliver intraductal collagenase immediately after excision of the pancreas before cold pancreas storage at 4°C. Studies in rats[8] have shown this technique to improve islet yields with administration of collagenase in Hanks balanced salt solution (HBSS), although HBSS is not a cold storage solution[9]. An improvement on this approach may be to deliver the collagenase in UW, immediately after excision of the pancreas and before cold storage. This procedure is effective in both dogs[10] and rats[10], but has been shown to be deleterious in humans because certain components of UW (e.g. glutathione, allopurinol, hydroxyethylstarch (HES) and the reversed sodium ion to potassium ion ratio) have an inhibitory action on collagenase[11–13]. Furthermore, porcine studies have been anecdotal[14,15]. The object of this study was to determine the influence on porcine islet isolation of intraductal collagenase administration, in cold storage solutions.

Materials and methods

Study design

Islet isolations were randomized using sealed envelopes to: (1) collagenase in HBSS either in the islet laboratory ($n = 8$) after cold pancreas storage, or in the local abattoir immediately after excision of the pancreas ($n = 8$) before cold storage; (2) collagenase in UW both in the islet laboratory ($n = 8$) and in the abattoir ($n = 8$) and (3) collagenase in a specially designed cold storage solution, University of Leicester solution (ULEIC) (*Table 1*) administered immediately after excision of the pancreas at the abattoir ($n = 8$) (*Fig. 1*).

Organ donors and procurement technique

Forty porcine pancreata were excised from 2–3-year-old Large White sows obtained from the local abattoir (Dawkins International, Congerstone, UK). Each pancreas was subjected to 10 min of warm ischaemia before excision. The splenic lobe (65–100 g) was excised on all occasions. Care was taken not to disrupt the pancreatic capsule or perforate the adjacent duodenum.

Collagenase distension

Each pancreas had intraductal administration of collagenase 1mg/ml in either HBSS[9] (Gibco, Life Technologies, Paisley, UK), UW[16] (Belzer UW-CSS; Du Pont, Wilmington, Delaware, USA) or ULEIC Of those distended in the laboratory (16 in total) each underwent approximately 65 min of cold ischaemia during pancreas transportation in HOC (Travenol, Thetford, UK) at 4°C[17]. Those assigned to early collagenase administration in the abattoir (24 in total) were also transported in HOC after distension of the pancreas with collagenase. The same batch of

Paper accepted 10 June 1996

Table 1 Composition of solutions used

	Collagenase solvent		
	HBSS	UW	ULEIC
Sodium (mmol/l)	141·0	20·0	131·0
Potassium (mmol/l)	6·0	140·0	3·9
Hydroxyethylstarch (g/l)		50·0	
Raffinose (mmol/l)		30·0	30·0
Dextran-40 (mmol/l)			0 2
Lactobionate (mmol/l)		100·0	100·0
Magnesium (mmol/l)	0·8	5·0	5 0
Bicarbonate (mmol/l)			
Chloride (mmol/l)	137·0	10·0	
Phosphate (mmol/l)	0·8	25·0	25·0
Sulphate (mmol/l)		5·0	
Glucose (mmol/l)	5·6		
Adenosine (mmol/l)		5·0	
Allopurinol (mmol/l)		1·0	
Glutathione (mmol/l)		3·0	
Insulin (mmol/l)		100 0	
Dexamethasone (mmol/l)		8·0	
Calcium (mmol/l)	1·3		2·4
Osmolarity (mmol/kg)	300·0	320·0	289·0
pH	7·3	7·4	7·0

HBSS, Hanks balanced salt solution; UW, University of Wisconsin solution; ULEIC, University of Leicester solution

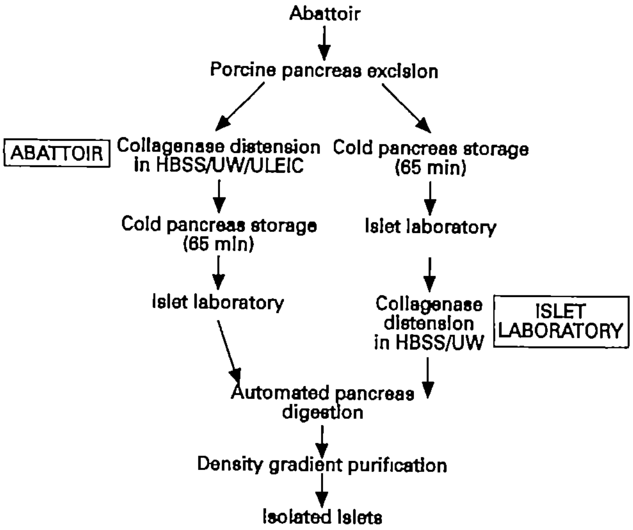
Abattoir
Porcine pancreas excision
ABATTOIR
Collagenase distension in HBSS/UW/ULEIC
Cold pancreas storage (65 min)
Cold pancreas storage (65 min)
Islet laboratory
Islet laboratory
Collagenase distension in HBSS/UW
ISLET LABORATORY
Automated pancreas digestion
Density gradient purification
Isolated islets

Fig. 1 Flow chart of study design HBSS, Hanks balanced salt solution; UW, University of Wisconsin solution, ULEIC, University of Leicester solution

collagenase (lot no. 14039526-54; Boehringer, Mannheim, Germany) was used throughout the study. Before distension, excess fat and lymphoid tissue were removed. The pancreas was weighed and the main pancreatic duct was cannulated with an 18-G cannula (Abbocath-T; Abbot Laboratories, Kent, UK) secured by a 2/0 silk tie (Ethicon, Edinburgh, UK). Each pancreas was distended by slow injection of collagenase in solution at 4°C using 2 ml per g pancreas An evenly distended pancreas was obtained by gradual withdrawal of the cannula during infusion, any ductal leaks were immediately clamped with forceps.

Pancreatic digestion

All pancreata were digested by the automated method[3,18] The pancreas was placed in a stainless steel chamber divided by a 400-μm mesh, along with seven 1-cm^3 steel spheres to aid pancreatic dispersion. HBSS at 4°C was circulated through a closed circuit of polyvinyl chloride tubing (COBE Laboratories, Gloucester, UK) by a peristaltic pump (Watson Marlow, Falmouth, UK) set at a rate of 80 ml/min into a heat exchanger (COBE Laboratories) initially at 35°C. The chamber was manually agitated between two and three times per minute. Pancreatic tissue was flushed from the exit port of the steel chamber and then 5-ml samples were taken via a three-way tap and examined under a light microscope (Nikon, Diaphot, Japan) at × 4 magnification in the presence of dithizone (1·2 mmol/l in 5 per cent dimethylsulphoxide-minimal essential media (MEM) and 1 per cent bovine serum albumin (BSA)[19] (Sigma Chemicals, Poole, UK) for identification of 'cleaved' islet tissue devoid of acinar tissue At this point the circuit was opened and the flow rate increased to 120 ml/min. The temperature was adjusted according to visualization of pancreatic tissue within the biopsies to avoid fragmentation and overdigestion as islets were liberated[20]. The digest was collected in 1-litre Duran bottles containing 15 ml new born calf serum (Advanced Protein Products, Brierly Hill, UK) to inhibit further action of collagenase[21] The collected tissue was washed and spun at 600*g* for 2 min and made up to a volume of 100 ml with UW at 4°C Pancreatic digestion was assumed to be complete when no further islet tissue could be seen within the dithizone-stained samples.

Islet quantification

After 30 min of prepurification storage in 100 ml UW[22,23], five samples of 100 μl were taken from the resuspended pancreatic digest and individually placed in bijoux containing 0·9 ml MEM (Northumbria Biologicals, Cramlington, UK). From each of these five bijoux, single 100-μl strips were aspirated and stained with dithizone in a 140-mm petri dish giving a total dilution of 1 : 10 000. The number of islets totally devoid of acinar tissue (cleaved) and the number still attached to acinar tissue (uncleaved) with a diameter greater than 50 μm, within each strip, were counted under a light microscope (× 100 magnification) calibrated with an optical grid (Cell Finder, Leiden, Holland)[7,18]. This allows estimation of the percentage of cleaved and uncleaved islets along with the total number of islets per gram of pancreas. To calculate the total volume of islet tissue and the mean volume of an islet, 200 consecutive islet diameters were recorded from each of the 40 pancreatic digests. The total volume of islet tissue isolated was calculated as the product of the mean volume of an islet and the total number of islets[7,18].

Having calculated the mean islet diameter from 2–3-year-old Large White sow pancreas to be 80 μm using computerized image analysis (Improvision, Coventry, UK)[24], islet yields were corrected to Large White porcine islet equivalents (IEQ) by dividing the total volume of islet tissue by the volume of an 80-μm porcine islet ($0{\cdot}524 \times (80)^3$), assuming that islets are spherical. This correction, therefore, equates to the 150-μm equivalents reported for human pancreata and allows a more accurate assessment of the isolation index[18,24].

Islet purification

A 3-ml sample of the pooled digest was spun at 600*g* for 2 min A 65-μl aliquot of this packed sample digest was placed in duplicate 10-ml test tubes containing 1 ml high-density BSA (Advanced Protein Products). This was then overlaid with a 10-ml continuous linear gradient of BSA by a two-chamber gradient maker containing 5·2 ml low-density BSA and 5·2 ml high-density BSA (5 2 ml in each chamber to allow for losses within the gradient maker) mixed together with a magnetic flea (Hoefer Scientific Instruments, San Francisco, California, USA). The high-density BSA and low-density BSA were 1·103 g/cm^3 and

1·075 g/cm^3 respectively, following dilution with MEM and measurement with a densitometer (Paar Scientific, London, UK). The final osmolarity was corrected to 400 mosmol per kg H_2O for both high- and low-density BSA by dilution with sodium chloride upon titration with a vapour pressure osmometer (Chem Lab Scientific Products, Hornchurch, UK). The two synchronously produced minigradients were centrifuged at 500*g* for 5 min at 22°C to allow the digest to equilibrate at its isodense point on the gradient. Eleven 1-ml aliquots were then aspirated in successive order from the meniscus of each tube. Each aliquot was washed twice with 3 ml MEM and finally resuspended in a further 2 ml[23,25]. They were then sonicated for three periods of 30 s on ice; 1 ml was aspirated for assay of amylase content (Phadebas amylase test kit; Pharmacia Diagnostics, Uppsala, Sweden) and a further 1 ml mixed with 1 ml Ziegler reagent[26] for subsequent enzyme-linked immunosorbent assay (ELISA) (Medgenix-INS-EASIA; Medgenix Diagnostics, Fleurus, Belgium) of insulin content. The cumulative percentages of the insulin and amylase content within the gradient fractions were plotted against density (Cricket Graphs, Malvern, Pennsylvania, USA) to ascertain the percentage amylase contamination of a 60 per cent insulin yield, deemed to be a reasonable yield of islets[22–25].

Islet viability

Following large-scale purification on a COBE 2991 processor (COBE Laboratories)[27] the viability of islets isolated from five pancreata from each of the five different groups was assessed by *in vitro* dynamic incubation[20]. Five groups of ten islets were hand-picked from each preparation using a drawn-out Pasteur pipette, following 48 h of postpurification culture in Hams-F-12 medium[28,29] at 37°C. They were transferred, in as little medium as possible, to 200 μl low-glucose (1·7 mmol/l, prepared by 1 : 3 dilution with balanced electrolyte solution) RPMI (Gibco) prewarmed to 37°C and placed in a 1·5-ml microcentrifuge tube. The islets were then left to incubate in a shaking water bath at 37°C for 45 min. The 200-μl supernatant was then removed and replaced by a further 200 μl low-glucose RPMI for 1 h then high-glucose (25 mmol/l) RPMI for 1 h and finally with low-glucose (1·7 mmol/l) RPMI for 1 h as described previously[20]. The insulin content within the supernatant of each of the final two phases was measured by ELISA. Stimulated insulin release was expressed in microunits per islet per hour, calculated as the difference between insulin content in the high-glucose response and the final low-glucose response[20,28].

Statistical analysis

Results are expressed as median (range). Differences between each of the five groups were analysed initially by Kruskall–Wallis one-way analysis of variance. Comparisons between pairs were then made, where valid, using the Mann-Whitney *U* test with its significance (adjusted for ties) being expressed as a *P* value. In addition, the 95 per cent confidence interval (c.i.) for differences between the groups was reported where appropriate (Minitab release 8.1; State College, Pennsylvania, USA).

Results

Pancreas digestion

Results for the five different groups are given in *Table 2*, and *Figs 2–4*. There were no significant differences between the groups with respect to weight of pancreas (range 59–110 g) and cold ischaemia time (range 48–99 min). The volume of digest differed significantly, with median values ranging from 0·18 to 0·34 ml/g ($P = 0{\cdot}01$). This was mainly attributable to the increased volume of pancreatic digest following administration of collagenase in UW at the abattoir (median 0·34 ml/g), compared with that after conventional collagenase administration in HBSS at the islet laboratory (median 0·18 ml/g) ($P = 0{\cdot}01$; 95 per cent c.i. −0·24, −0·04). This trend also reflects the significantly greater volume of islet tissue ($P = 0{\cdot}01$) and islet equivalents isolated ($P = 0{\cdot}02$). Median values ranged between 3·55 and 11·02 mm^3/g for volume of islet tissue (*Table 2*), and 6924 and 21 524 IEQ/g for islet yield (*Fig. 2*). When collagenase was administered in UW at the abattoir, islet yields were trebled compared with those obtained with HBSS at the islet laboratory (median 6924 *versus* 21 524 IEQ/g; $P = 0{\cdot}02$; 95 per cent c.i. −33 554, −508) (*Fig. 2*). Collagenase administration in ULEIC at the abattoir was also shown to be superior to the conventional method of delivery in HBSS in the laboratory ($P = 0{\cdot}003$; 95 per cent c.i. 6347, 18 867). When collagenase was administered in ULEIC, islet yields were similar to those of collagenase administration in UW at the abattoir (median 19 814 *versus* 21 524 IEQ/g; $P = 1{\cdot}0$; 95 per cent c.i. −11 699, 20 762) (*Fig. 2*). Finally, the differences between islet–acinar cleavage index and mean volume of an islet were not statistically significant (*Table 2*).

Density gradient purification and stimulated insulin release

BSA continuous density gradient purification studies demonstrated a range of median values of amylase contamination at a 60 per cent insulin yield between 9 and

Table 2 Summary of results

	Islet laboratory		Abbatoir			
	HBSS ($n = 8$)	UW ($n = 8$)	HBSS ($n = 8$)	UW ($n = 8$)	ULEIC ($n = 8$)	*P**
Cold ischaemia (min)	68 (56–88)	63 (52–99)	59 (48–71)	61 (56–67)	69 (61–77)	0·70
Weight of pancreas (g)	80 (71–95)	75 (60–110)	67 (59–92)	79 (62–88)	71 (63–77)	0·50
Pancreatic digest volume (ml/g)	0·18 (0·09–0·29)	0·20 (0·03–0·27)	0·21 (0·04–0·24)	0·34 (0·22–0·45)	0·23 (0·16–0·37)	0·01
Cleavage index (%)	53 (48–71)	67 (52–75)	58 (28–79)	63 (42–70)	57 (38–72)	0·15
Total volume islet tissue (mm^3/g)	3·55 (0·72–6·6)	4·53 (1·61–9·84)	7·14 (0·40–27·69)	11·02 (3·80–29·85)	10·15 (5·38–16·26)	0·02
Mean volume of an islet $\times 10^{-4}$ (mm^3)	5·18 (1·44–12·61)	4·10 (1·63–12·60)	7·00 (1·72–26·90)	6·29 (1·68–10·80)	7·74 (4·44–21·02)	0·40

Values are median (range). HBSS, Hanks balanced salt solution; UW, University of Wisconsin solution; ULEIC, University of Leicester solution. *Kruskall–Wallis one-way analysis of variance

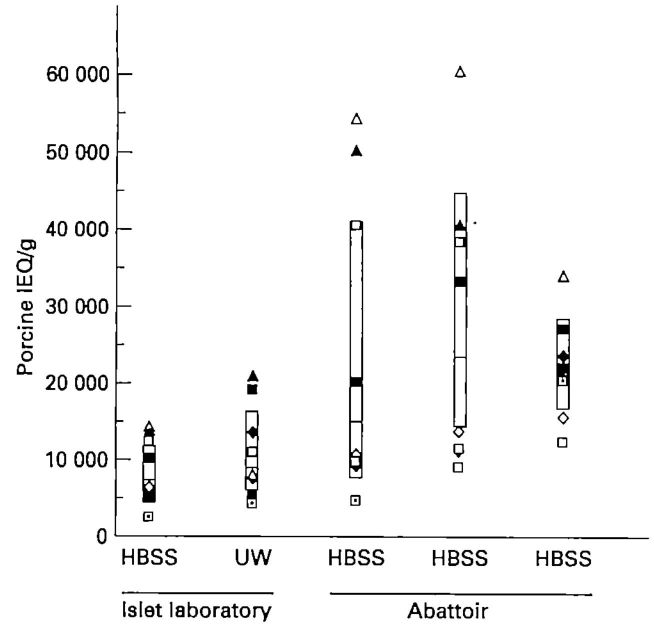

Fig. 2 Islet yields from different isolation protocols as defined in text. Boxes are median (95 per cent confidence interval (c.i.)). IEQ, islet equivalent based on 80-μm diameter porcine islet, HBSS, Hanks balanced salt solution; UW, University of Wisconsin solution; ULEIC, University of Leicester solution. $P = 0{\cdot}04$ (95 per cent c.i. $-33\,554$, -508), HBSS (laboratory) *versus* UW (abattoir); $P = 0{\cdot}01$ (95 per cent c.i. 6347, 18 867), HBSS (laboratory) *versus* ULEIC (abattoir) (Mann–Whitney *U* test)

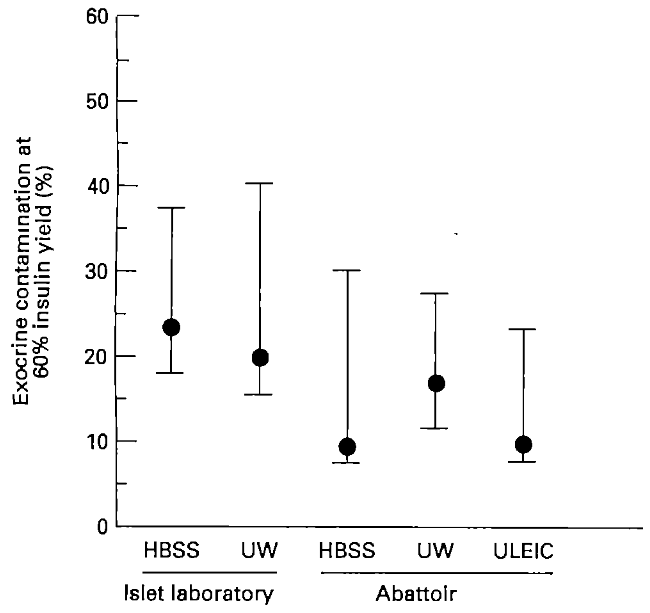

Fig. 3 Exocrine contamination of islets isolated in various solutions (see text). Boxes are median (95 per cent confidence interval). HBSS, Hanks balanced salt solution; UW, University of Wisconsin solution; ULEIC, University of Leicester solution. $P = 0{\cdot}32$ (Kruskall–Wallis one-way analysis of variance)

24 per cent, none of which differed significantly ($P = 0{\cdot}32$; *Fig. 3*). There was no difference in glucose-stimulated insulin release after administration of collagenase in either UW or ULEIC compared with that in appropriate controls ($P = 0{\cdot}43$; *Fig. 4*).

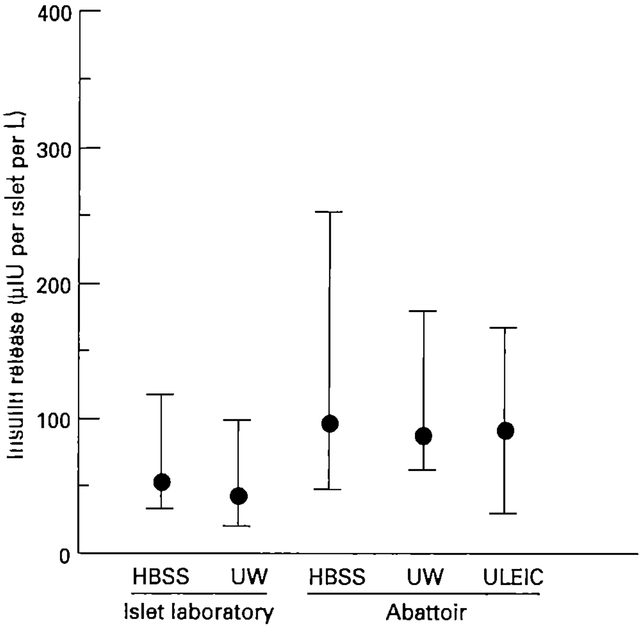

Fig. 4 Stimulated insulin release in islets isolated in various solutions (see text). Boxes are median (95 per cent confidence interval). HBSS, Hanks balanced salt solution; UW, University of Wisconsin solution; ULEIC, University of Leicester solution. $P = 0{\cdot}43$ (Kruskall–Wallis one-way analysis of variance)

Discussion

It is well established that short periods of cold pancreas ischaemia before islet isolation are deleterious to both yield[30–32] and viability[33] of islets. Even after as little as 3 h of cold pancreas ischaemia, canine islet yields have been shown to be significantly reduced[30]. In an attempt to improve cold ischaemic tolerance of rat pancreas Ohzato *et al.*[8] demonstrated the benefit of early intraductal collagenase administration in HBSS solution at the time of harvesting. Munn *et al.*[10] were the first to describe the technique of collagenase administration in a cold storage solution using a modified UW in both rats and dogs. It was shown that preservation with modified UW and collagenase before islet isolation maintained islet yields for up to 24 h. The results in this study confirm this hypothesis in the pig, in that regardless of the cold storage solution used, islet yields were markedly improved by intraductal collagenase distension immediately after harvesting and before any period of cold pancreas ischaemia.

However, in humans a number of reports have suggested an adverse affect of UW[7,12,13]. Indeed, the authors have reported recently that UW is inhibitory to human but not to adult porcine pancreas digestion[13] and could ideally be used, therefore, as a solvent for early intraductal collagenase administration to ameliorate cold pancreas ischaemic damage subsequent to porcine islet isolation.

Notwithstanding the benefits of UW for porcine islet isolation, it is an expensive and complex solution. Indeed, some of the additives are thought not to be crucial for its success in preservation of liver[34], kidney[35] and pancreas[36]. Studies in this laboratory[13,23,37] have indicated that adenosine, allopurinol, glutathione and the reversed sodium ion to potassium ion are not essential for cold storage of pancreatic tissue. The key components of UW considered to be of benefit are the impermeants raffinose and lactobionate along with the expensive synthetic colloid[38,39] used to reduce cellular swelling. While the role of impermeants is well established, that of HES is less well understood[36]. For preservation of both canine kidneys and pancreas[36] results have been as effective when HES is replaced with cheaper additives such as dextran-40. Studies of porcine islet isolation also support this finding[37]. Moreover, studies of human islet isolation have shown some degree of collagenase inhibition by HES perhaps by altering the configuration of the active site of collagenase[13,40], although porcine islet isolation remains unaffected[13]. ULEIC was therefore designed specially to contain only those components considered beneficial to cold pancreas storage before islet isolation. The main components are lactobionate, raffinose, dextran-40 and a physiological sodium ion to potassium ion ratio.

The findings from this study suggest that UW or ULEIC have no inhibitory action on collagenase digestion compared with controls. No significant difference could be demonstrated between any of the five groups in terms of islet purification or islet viability *in vitro*, although the ultimate assessment of long-term islet viability *in vivo* would be by porcine islet autotransplantation, however, success has rarely been achieved with that model and *in vitro* function was chosen as an end point[41]. In summary, therefore, early collagenase delivery at the abattoir in any solution before cold pancreas ischaemia was necessary for greater islet yields. Significantly better islet yields were achieved with collagenase administered in UW or ULEIC immediately before cold pancreas ischaemia than with the conventional method of collagenase delivery at the islet laboratory in HBSS following cold pancreas ischaemia. The potential benefit of UW and ULEIC before cold pancreas ischaemia may become more apparent following a longer duration of cold ischaemia.

Acknowledgements

The financial support of The British Diabetic Association, NovoNordisk UK and The Nuffield Hospitals Trust is acknowledged.

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British Journal of Surgery 1996, 83, 1356–1360

Incidence and nature of bile duct injuries following laparoscopic cholecystectomy: an audit of 5913 cases

M. C. RICHARDSON, G. BELL*, G. M. FULLARTON and THE WEST OF SCOTLAND LAPAROSCOPIC CHOLECYSTECTOMY AUDIT GROUP

*Department of Surgery, Gartnavel General Hospital, Glasgow and *Surgical Unit, Inverclyde Royal Hospital, Greenock, UK*

Correspondence to: Mr G M. Fullarton, Department of Surgery, Gartnavel General Hospital, 1053 Great Western Road, Glasgow G12 0XN, UK

The rapid introduction of laparoscopic cholecystectomy has been associated with an apparently increased incidence of bile duct injury which has provoked worldwide concern. The true incidence and mechanism of iatrogenic ductal injury during the development of this procedure remain unclear. To assess this, the introduction of laparoscopic cholecystectomy in the West of Scotland has been audited prospectively over a 5-year period. All cases of biliary ductal injury have been independently reviewed. Some 48 surgeons undertaking laparoscopic cholecystectomy in 19 hospitals submitted prospective data between September 1990 and September 1995. A total of 5913 laparoscopic cholecystectomies were attempted with 98·3 per cent completion of data collection. During this period 37 laparoscopic bile duct injuries occurred. The annual incidence peaked at 0·8 per cent and has fallen to 0·4 per cent in the final year of audit. Injuries occurred after a median personal experience of 51 (range 3–247) laparoscopic cholecystectomies in 22 surgeons. Major bile duct injuries occurred in 20 of 37 patients, giving an incidence of 0·3 per cent. Five mechanisms for laparoscopic ductal injury were identified, including tenting, confluence and diathermy injuries as well as the classical and variant classical types. Ductal injuries were discovered at operation in 18 patients with consequent repair giving a good clinical outcome in 17. Contributory factors (severe inflammation, aberrant anatomy and poor visualization) were present in only 13 of 37 cases. This audit suggests that, at least in the introductory period, laparoscopic cholecystectomy is associated with an overall bile duct injury rate higher than that reported previously after open cholecystectomy, although the incidence of major ductal injury is similar. The late downward trend in bile duct injury, however, suggests there may be a prolonged learning curve for this procedure. Improved understanding of the mechanism of injury may lead to yet further reductions in this complication.

Since its introduction in the late 1980s laparoscopic cholecystectomy has rapidly become the procedure of choice in the treatment of symptomatic cholelithiasis[1]. Unfortunately, the obvious advantages for the majority of patients have been somewhat tempered by the apparently increased risk of bile duct injury compared with that of open cholecystectomy[2], for which historical and contemporary series report the incidence of iatrogenic injury at 0–0·5 per cent[3–7]. The bile duct injury rates for laparoscopic cholecystectomy have been reported to be between 0 and 1·2 per cent, with considerable variation between single-centre and multicentre series[8–16]. The true incidence of biliary injury following laparoscopic cholecystectomy remains unclear, however, because of uncertainties in pick-up rates within retrospective series.

Investigation of the nature of bile duct injury following laparoscopic cholecystectomy has suggested that there is a more severe ductal injury pattern than has been recognized in open cholecystectomy[17–26]. As yet, however, a comprehensive classification does not exist and therefore formal description of the type and mechanism of injury remains difficult.

This audit endeavours to give a definitive overview of the incidence and type of laparoscopic bile duct injuries occurring in the West of Scotland. A classification system for mechanism of injury is proposed on the basis of these findings.

Patients and methods

The West of Scotland region serves a population of 2 422 130 people, supplying healthcare in 19 hospitals. These include 15 National Health Service (six teaching, nine district general) and four private hospitals. The West of Scotland Laparoscopic Cholecystectomy Audit Group was established in September 1990, at the inception of this procedure in the region. All consultant surgeons were enrolled into the audit as they undertook their first laparoscopic cholecystectomy; a total of 48 surgeons was involved. This represented all surgeons providing a laparoscopic cholecystectomy service within these hospitals.

Prospective data were submitted by the operating surgeon on all patients undergoing cholecystectomy A standard pro forma including demographic information, operative details and postoperative course was subsequently reviewed by a dedicated research nurse, who validated the data from individual patient case records. Complete audit was assured by review of all operating theatre records within the region[27].

All cases of laparoscopic bile duct injury identified were individually reviewed by the first author. Full casenote and radiological review has been supplemented by frank discussion of the cases with the surgeons involved. Bile duct injuries were defined as iatrogenic trauma to the hepatic ducts or common bile duct. Inadvertent injury to the cystic duct stump or postoperative bile leaks from other sources were not included. For the purposes of this study injuries were subclassified by severity into major and minor injuries (*Table 1*)[28].

Results

A total of 5913 laparoscopic cholecystectomies were performed in the West of Scotland between September 1990 and September 1995. Overall, this constituted 78·6

Paper accepted 30 May 1996

Table 1 Proposed definition of major and minor bile duct injuries

Grade	Description
Major	Laceration of more than 25 per cent of the bile duct diameter
	Transection of the CHD or CBD
	Development of postoperative bile duct stricture
Minor	Laceration of less than 25 per cent of the bile duct diameter
	Laceration of the junction of the cystic duct with the CBD ('buttonhole' tear)

CBD, common bile duct; CHD, common hepatic duct

per cent of the 7525 cholecystectomies performed during this period. Of those attempted laparoscopically, 5091 were completed and 822 (13·9 per cent) required conversion to an open procedure. Data collection and validation is 98·3 per cent complete; there are 101 case sheets outstanding.

In the 5913 attempted laparoscopic cholecystectomies within this audit there were 37 laparoscopic bile duct injuries, with an overall incidence of 0·6 per cent. The annual incidence peaked at 0·8 per cent and has fallen to 0·4 per cent in the final year of audit (*Fig. 1*). Notably, there were no deaths secondary to bile duct injury within this series. However, 26 patients required prolonged hospital admission and 14 required a further operative procedure.

During this period, 22 surgeons incurred a median of 1 (range 1–5) bile duct injuries after a median of 51 (range 3–247) laparoscopic cholecystectomies. The incidence of bile duct injury therefore varied between 0·4 and 4 per cent for the individual surgeons involved. A consultant surgeon was implicated as the primary operator in 27 patients with a consultant-supervised trainee being responsible in the other ten.

Of the bile duct injuries in this series 20 of 37 were considered major (*Table 1*). The incidence of major bile duct injury was, therefore, 0·3 per cent. This group comprised nine major lacerations or transections of the common bile duct, eight severe injuries to common hepatic ducts including three cases of significant trauma to the confluence, one major right hepatic ductal laceration and two late strictures at the level of the cystic duct insertion. A further 17 bile duct injuries were deemed minor, consisting of 'buttonhole' tears and small lacerations. These involved common bile duct in nine patients, common hepatic duct in six and right hepatic duct in two. The pattern of injury is illustrated in *Fig 2*.

Ductal injuries were discovered at the time of laparoscopic cholecystectomy in 18 patients involving seven major and 11 minor injuries. A total of 13 of these injuries involved the common bile duct with a single recognized injury to the common hepatic duct. In two patients with an acutely inflamed gallbladder the confluence of the hepatic ducts was clipped and divided and a further two injuries were caused by inadvertent partial clipping of the hepatic duct whilst clipping the cystic duct.

Delayed identification of bile duct injury occurred in 19 patients; 13 injuries were major and six minor. Within this group only five injuries involved the common bile duct; 14 patients had trauma to the hepatic ducts. Sixteen patients presented with postoperative bile leaks, four in combination with jaundice, and three experienced jaundice alone

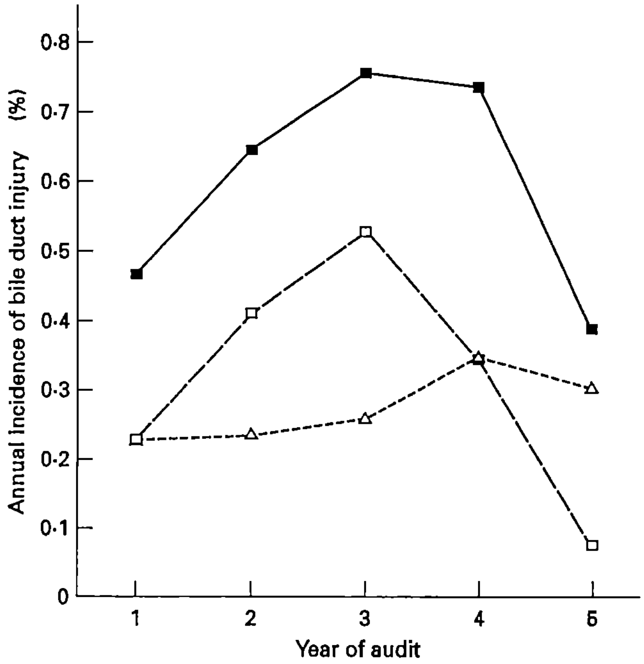

Fig. 1 Annual incidence of laparoscopic bile duct injury. ■, Overall; □, major bile duct injury; △, minor bile duct injury

Contributory factors

Contributory factors that have previously been implicated in laparoscopic bile duct injuries were present in only 13 patients. They included severe inflammation (seven patients), aberrant anatomy (four) and poor visualization (two). No significant contributory circumstances could be identified in the other 24 patients. Although individual surgeons involved had varying views on the exact mechanism of injury, the majority cited misidentification of anatomy as an important contributory factor. Obscured view secondary to bleeding, bile leakage, intervening tissue and suboptimal placement of ports or insufflation played a variable part in structures being incorrectly identified. Adhesion and fatty tissue around Calot's triangle were also quoted as less important factors.

Operative cholangiography was performed on a selective basis by most surgeons; imaging was used in 8·8 per cent of procedures overall. Notably, cholangiography did not play a part in the identification of bile duct injuries in this series. One minor hepatic ductal injury occurred during clipping of the cystic duct following successful cholangiography, when both cystic duct and the adjacent wall of hepatic duct were clipped.

Discussion

The West of Scotland series represents a large comprehensive review of laparoscopic cholecystectomy practice within a geographically defined region. As data collection was prospective, 98·3 per cent complete and subsequently validated by an independent research nurse, it reflects a highly accurate overview of the introduction of this technique.

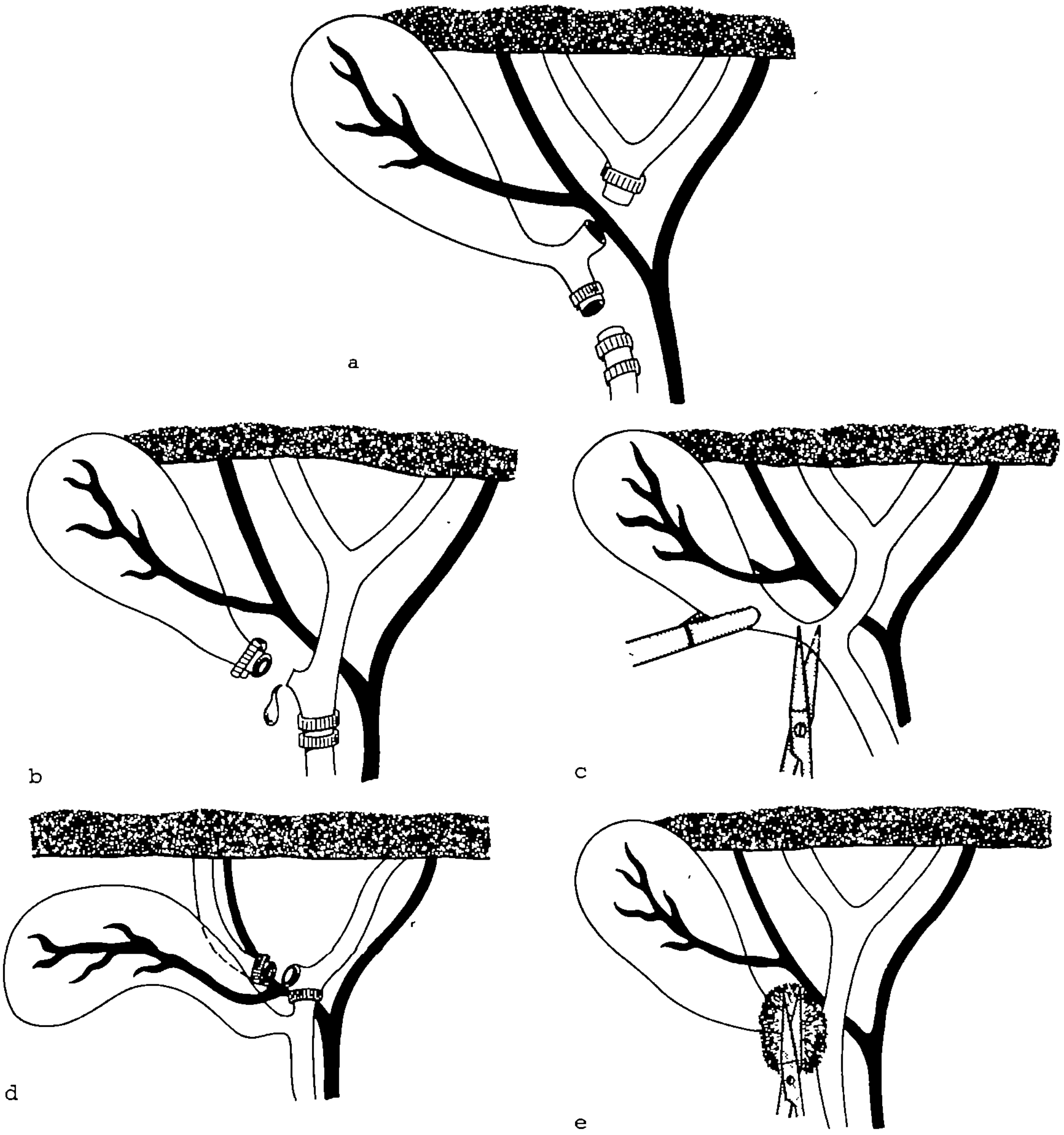

Fig. 2 **a** 'Classical' injury (seven of 37 cases): misidentification of the common bile duct for the cystic duct with resultant clipping and division of the common duct and resection of a segment of common hepatic duct. Underlying right hepatic arterial injury associated. **b** 'Variant classical' injury (three cases): incorrect identification of common bile duct for proximal cystic duct with clipping. Upper cystic duct identified correctly, clipped and divided, leading to a bile leak. **c** 'Tenting' injury (17 cases): lateral traction of gallbladder causes tenting of common duct with loss of angle of interception with cystic duct. Dissection low on cystic duct leads to inadvertent laceration (or clip involvement) of the common duct at this junction. **d** 'Confluence' injury (five cases): misidentification of right hepatic duct for cystic duct. Clipping and division around the confluence results in a high, severe injury. **e** 'Diathermy' injury (five cases): injudicious use of diathermy in Calot's triangle with resultant bile leak (necrosis) or late stricture

The overall conversion rate of 13·9 per cent is somewhat higher than that reported in many previous series[16,29–31] but probably reflects that this audit commenced at the very introduction of laparoscopic cholecystectomy to the region. It is, however, comparable to the overall conversion rates noted in randomized controlled trials and other British series[2,15,32]. By encompassing a broad spectrum of surgeons as they first introduced the technique this series represents the laparoscopic learning period. Although the conversion rate remains relatively constant over the audit period it shows a significant reduction for the more experienced laparoscopic surgeons.

An overall laparoscopic bile duct injury rate of 0·6 per cent in this audit compares unfavourably with an incidence of 0–0·5 per cent for iatrogenic injuries in historical and more recent reviews of open cholecystectomy[3–7]. However, a recent large audit of current cholecystectomy practice from Canada has, in fact, shown a higher incidence of bile duct injury at 2·1 per cent after open cholecystectomy compared with 0·7 per cent after laparoscopic cholecystectomy[16]. This increased bile duct injury rate after conventional cholecystectomy may reflect more complex cases currently being subject to open procedure. Most of the available figures arise from retrospective voluntary reporting and therefore may underestimate the true incidence. Whether the precise definition of bile duct injury used in this study has been rigorously applied in retrospective open cholecystectomy series remains open to question. It may well be that the incidence of bile duct injuries that should be used for comparison is that for major laparoscopic bile duct injuries, which stands at 0·3 per cent in this series, and is therefore similar to that reported at open cholecystectomy. In fact in the final year of this audit the major bile duct injury rate was less than 0·1 per cent.

The incidence of laparoscopic bile duct injury has been reported to be between 0 and 1 per cent[8–14,16] with a wide range in early series being explained by small numbers and a relatively low incidence[13,33,34]. More recently large single-centre cohorts have often demonstrated local expertise and therefore report a lower rate than that seen in this complete regional audit[8,35,36], although a recent smaller but complete study in the UK has suggested an even higher incidence of laparoscopic bile duct injury at 1·2 per cent[15]. Large multicentre series reported previously mainly reflect retrospective review of voluntary data, without accurate validatory mechanisms, and consequently must be viewed with a degree of caution[9,10,12,14,26].

The incidence of bile duct injury in the West of Scotland appears to have peaked at around 0·8 per cent and fallen to 0·4 per cent towards the end of the audit period, showing a delayed trend when compared with previous reports[12,26,30,37]. The suggested short learning curve with clustering of injuries in the first few cases has not occurred. The learning curve in laparoscopic cholecystectomy therefore appears prolonged and correlates with that seen for the open procedure, where the expected danger period lies between 25 and 100 cases[38]. However, as laparoscopic iatrogenic injuries have occurred across the whole spectrum of experience, continued vigilance is imperative.

The bile duct injury pattern after laparoscopic cholecystectomy appears to be more severe than that noted for open cholecystectomy where minor injuries are thought to predominate[17–26]. Based on the proposed classification system, major injuries account for 54 per cent of the total (20 of 37) in this series. However, the incidence of minor ductal trauma (17 of 37; 46 per cent) is higher than has been alluded to in other series, suggesting a more comprehensive pick-up.

Several attempts have been made to classify bile duct injuries in an effort to define the underlying mechanisms although no formal classification system exists. The higher incidence of minor injuries in this audit has altered the overall pattern of injuries seen (*Fig. 2*). Previously most injuries were considered to be 'classical' or 'variant classical' as initially described by Davidoff *et al.*[18]. These types account for only ten of the injuries seen in this series, in which a less severe 'tenting' injury predominated (17 patients). This injury occurred when marked lateral traction was applied to Hartmann's pouch with consequent tenting of the common duct. Loss of the angle of intersection between the cystic duct and common duct led to inadvertent injury when dissection was carried out around the junction.

Although high biliary injuries have been described, little is known about the mechanism by which they occur except for misidentification of ductal structures. In this audit, so-called 'confluence' injuries usually occurred in association with severe inflammation (acute cholecystitis or empyema) and an attempt at retrograde dissection. In these circumstances, the right hepatic duct was identified incorrectly as the cystic duct, with subsequent clipping and division leading to a severe injury around the confluence of hepatic ducts. This mechanism accounted for five of the injuries seen.

Diathermy has been highlighted previously as a cause of iatrogenic injury but was thought to be responsible for only five of the injuries within this audit. Inadvertent use of diathermy within Calot's triangle close to the common duct led to postoperative stricture in two patients and bile leaks from small perforations in the hepatic duct in a further three.

Although contributory factors were found to be present in a minority of cases, the majority of injuries were secondary to misidentification of anatomy. Tenting of the common duct was implicated in most of the injuries, frequently in association with dissection low on the cystic duct. Based on these findings, the authors advocate the following measures to avoid laparoscopic bile duct injury.

Meticulous identification of anatomy is essential, with clear identification of the anatomy in Calot's triangle before clipping of the cystic duct and artery. This is optimized by dissection of the posterior biliary space to free the neck of the gallbladder from the liver bed in conjunction with adequate demonstration of the junction of gallbladder neck and cystic duct (particularly with retrograde dissection).

Lateral traction on Hartmann's pouch is thought to open Calot's triangle and create a sharper angle between cystic duct and common bile duct but, in fact, may distort and conceal this angle by tenting. Therefore, when significant lateral traction is applied, dissection where possible should be close to the gallbladder and high on the cystic duct. If dissection lower on the cystic duct is necessary this should preferably be blunt with minimal use of diathermy in this region and also within Calot's triangle. If any of the above measures are compromised, early conversion to open cholecystectomy is suggested.

Another feature of laparoscopic ductal injuries has been late recognition with consequent increased severity of injury. This audit reports a higher incidence of peroperative identification compared with previous laparoscopic series (18 of 37 injuries) with the suggestion that early repair leads to an improved outcome[26]. There appears to be an upward trend towards earlier discovery and this may reflect increased vigilance secondary to published worldwide concern. Notably, trauma to the common bile duct appears easier to detect than injuries above the cystic duct.

In conclusion, this study suggests that at least in the introductory period the overall bile duct injury rate after laparoscopic cholecystectomy appears higher than that in open cholecystectomy series reported previously. Considering only major bile duct injuries, however, the overall rate is comparable to that of retrospective open cholecystectomy series. The late downward trend in the bile duct injury rate with experience of laparoscopic cholecystectomy suggests there may be a prolonged 'learning curve' in this procedure. Further reductions, approaching the incidence reported at open cholecystectomy, may be possible with greater understanding of the mechanism of injury.

Appendix

West of Scotland Laparoscopic Cholecystectomy Audit Group:

W. R. Murray, C. W. Imrie, J. R. Anderson, J. N. Baxter,

T. Cooke, *Glasgow Royal Infirmary, Glasgow G4 0SF;* P. O'Dwyer, G. Ramsay, *Western Infirmary, Glasgow G11 6NT;* D. Galloway, A. McKay, P. N. Rogers, *Gartnavel General Hospital, Glasgow G12 0YN;* J. S. Smith, D. T. Hansell, *Stobhill Hospital, Glasgow G21 3UW;* A. Litton, G. McBain, G. T. Sunderland, J. C. Ferguson, *Southern General Hospital, Glasgow G51 4TF;* A. Mack, D. C. Smith, I. S. Smith, G. Gillespie, G. Gray, J. K. Drury, *Victoria Infirmary, Glasgow G42 9TY.*

Districts: P. J. Shouler, E. W. Taylor, J. R. McCallum, *Vale of Leven District General Hospital, Alexandria G83 0UA;* G. Bell, J. J. Morrice, G. Orr, I. Watt, *Inverclyde Royal Hospital, Greenock PA16 0XN;* K. G. Mitchell, B. W. A. Williamson, *Royal Alexandra Hospital, Paisley PA2 9PN;* A. D. McNeill, A. Smith, W. S. Hendry, D. B. Booth, *Stirling Royal Infirmary, Stirling FK8 2AU;* C. Moran, B. A. Sugden, *Crosshouse Hospital, Kilmarnock KA2 0BE;* I. McKenzie, M. K. Browne, R. W. Brookes, *Monklands District General Hospital, Airdrie ML6 0JS;* J. Wallace, *Law Hospital, Carluke ML8 5ER;* H. Campbell, *Stonehouse Hospital, Stonehouse ML9 3NT;* D. G. Knight, J. R. Richards, J. R. Goldring, W. O. Thomson, *Hairmyres Hospital, Glasgow G75 8RG,* UK.

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British Journal of Surgery 1996, 83, 1361–1363

Day-case laparoscopic hernia repair

D. S. EVANS, P. GHANEH and I. M. KHAN

Department of Surgery, Royal Shrewsbury Hospital National Health Service Trust, Shrewsbury SY3 8XQ, UK
Correspondence to: Mr D. S. Evans

Some 114 patients (median age 52 years) underwent laparoscopic hernia repair as a day-case procedure. Twenty-one patients had bilateral and 11 recurrent hernias. Some 113 patients underwent transabdominal preperitoneal mesh repair but one required conversion to open operation. Mean operating time was 24 min for unilateral and 38 min for bilateral repair. In an operating session of 3·5 h, up to five patients (mean 4·4) underwent surgery and as many as seven hernias were repaired. More than 10 per cent of patients were found to have a previously undiagnosed hernia on the opposite side. A total of 111 patients were discharged home on the day of surgery. Major complications included one omental bleed and one small bowel obstruction. Seroma was the commonest minor complication and occurred in 7 per cent of patients. More than 35 per cent of patients needed no postoperative analgesia. To date there has been one recurrence (follow-up range 2–18 months).

Following the successful introduction of laparoscopic cholecystectomy, it was natural that other laparoscopic procedures would be developed. With the introduction of multiple stapling devices in 1992, many surgeons looked to laparoscopic repair of groin hernias.

Laparoscopic transabdominal preperitoneal mesh repairs began in this hospital in June 1992 and during the next 2 years the technique was refined. In June 1994, with experience of nearly 300 procedures and following the opening of a fully equipped and dedicated day surgical unit (DSU), day-case transabdominal preperitoneal mesh repair could be offered.

Patients and methods

Patients under the age of 70 years who were medically fit (American Society of Anesthesiologists grades I and II) and with suitable home circumstances for day surgery were admitted to the DSU. All patients had surgery under general anaesthesia. The operation was done in the Trendelenburg position with the arms by the side. A prophylactic antibiotic was given on induction of anaesthesia.

After establishing pneumoperitoneum with carbon dioxide the abdomen was entered through a transverse supraumbilical skin incision, either with a 10-mm reusable trocar blind or under direct vision using a Visiport (AutoSuture, Ascot, UK) or Optiview (Ethicon, Edinburgh, UK). The anatomy and pathology on both sides was then assessed at laparoscopy. Before insertion of the lateral ports, the abdominal wall was transilluminated to demonstrate the blood vessels[1]. For unilateral repairs the ipsilateral port was at the level of, and 5–7 cm lateral to, the umbilicus while the contralateral port was in the same position laterally but 2–4 cm inferior to the umbilicus. For bilateral repairs, both ports were placed level with the umbilicus.

Under laparoscopic vision the groin peritoneum was incised transversely and anterior to the defect from 2 cm lateral to the internal ring medial to the medial umbilical ligament. Hernia sacs were reduced or transected leaving the distal part of the sac *in situ*. The anatomy was then further defined and a pouch prepared extending from the symphysis pubis medially to at least 2·5 cm beyond the internal ring laterally. Posteriorly the peritoneum was dissected off the cord structures.

Polypropylene mesh, 12 × 7 cm or 15 × 10 cm, was inserted and positioned, with the medial border adjacent to the symphysis pubis and the inferior border placed well posteriorly to ensure complete cover of the myopectineal orifice. The mesh was then fixed in position, three staples were placed in the region of Cooper's ligament with further staples in the rectus muscle and transversalis fascia. No staples were placed posterior to the iliopubic tract. The peritoneum was double breasted and reconstituted by stapling or suturing, care being taken to ensure complete closure. It was particularly important to ensure that the posterior border of the mesh remained in position.

In some cases, to aid closure, the medial umbilical ligament was drawn laterally and stapled. For bilateral hernias, a similar procedure was done and a second mesh used. On completion of the repair, the lateral cannulas were removed and pneumoperitoneum maintained. The port sites were examined for any bleeding which was controlled, if necessary, by diathermy. In the elderly and those with thin abdominal wall musculature the lateral port sites were closed formally. The umbilical port was closed if a direct-vision cutting device had been used for entry.

On completion of the operation bupivacaine 0·5 per cent was injected around the port sites. Patients were allowed to recover and discharged home, usually within 4 h of completion of the operation. They were instructed not to drive for 48 h and not to lift heavy weights for 10 days. They were seen as outpatients after 2 weeks and subsequently contacted by mail or telephone to complete a questionnaire for review.

Results

In 15 months from June 1994, 114 patients underwent day-case hernia repair; all operations were done by a consultant. Median age was 52 (range 20–70) years and 103 patients were men. The procedure was unilateral in 93 patients and bilateral in 21. The majority of the hernias were indirect (*Table 1*) but included recurrent and sliding hernias and a number of patients with inguinoscrotal sacs. Mean duration of operation (skin incision to final stitch)

Table 1 Type of hernia in 114 patients

	n
Inguinal hernia	
Indirect	70
Direct	53
Recurrent	11
Sliding	11
Pantaloon	8
Femoral hernia	3

There were 21 bilateral hernias

Paper accepted 16 July 1996

Table 2 Complications in 114 patients undergoing 135 laparoscopic hernia repairs

	No. of patients
Major	
Omental bleed	1
Small bowel obstruction	1
Minor	
Sac seroma	8
Bruising – scrotal or groin	4
Port-site bleed	1
Port-site infection	1
Groin discomfort or pain	16

was 24 (range 15–60) min for unilateral and 38 (range 30–60) min for bilateral repair. During an operating session of 3·5 h, up to five patients (mean 4·4) underwent surgery and as many as seven hernias were repaired.

One patient with an irreducible hernia required conversion to open operation, while in 113 patients laparoscopic repair was completed. Some 111 patients were discharged from hospital the same day. One patient with a minor port bleed was admitted for overnight observation. No active treatment was required and he was discharged the following day. Another patient, in whom a different model of laparoscopic inflator was being assessed, suffered a minor omental bleed and had a minilaparotomy to secure haemostasis. He was discharged 3 days after operation. Two patients were readmitted more than 48 h after operation, one with pain in the groin on the operated side. This settled spontaneously overnight. The other proved to have subacute obstruction due to an internal hernia, secondary to the peritoneal closure. The medial umbilical ligament had been drawn laterally and stapled anteriorly to complete the closure. This had left a pocket with the opening inferolaterally into which small bowel had herniated. The patient had further laparoscopic surgery and the small bowel was reduced. The pocket was closed by suture and the patient then made an uneventful recovery, returning home 48 h after surgery.

Other complications were minor and transient (*Table 2*), the most common being sac seroma in 7 per cent of patients. Recovery was without complication in 84 per cent. To date, there has been one recurrence. This was repaired laparoscopically 1 year after the first operation.

Nine patients were listed for bilateral hernia repair. At operation a further 12 (10 per cent) were found to have a significant contralateral defect which required repair.

No analgesia was taken in hospital after operation. Following discharge no analgesia was necessary in more than 35 per cent of patients. The remainder required oral analgesia for a mean of 2 days. Analgesia requirement was not related to type or number of hernias repaired.

Some 93 per cent of patients were contacted by mail or telephone 2–18 months after operation and answered a questionnaire concerning satisfaction with the procedure, state of the repair and in particular whether there was any groin bulge or discomfort. More than 90 per cent expressed satisfaction with the procedure carried out in the DSU.

Two patients complained of a groin bulge and thought the repair was unsound. Outpatient review, however, showed no sign of recurrence. Some 85 per cent of patients had had no problems after the outpatient appointment held 2 weeks after operation, while the remainder complained of mild discomfort or stiffness.

Discussion

In accordance with the Royal College of Surgeons of England guidelines[2], 54 per cent of all patients under the same consultant undergoing hernia repair in the 15 months reviewed had day-case surgery. The low complication rate and rapid recovery from operation has enabled an increasing number of patients to have day-case hernia repair. The DSU opened in this hospital when there was already experience with nearly 300 transabdominal preperitoneal mesh repairs. The incidence of complications compared favourably with that in other series[3]. In comparison with open techniques operating times were equal if not shorter, the high throughput of cases being attributable to particular individual anaesthetic and nursing staff[4–6].

All types of hernia, including bilateral and recurrent defects, were suitable; the only difficulty arose with a hernia that was irreducible despite attempted reduction with a combined approach of laparoscopic dissection and external manual compression. Some 98 per cent of patients were discharged home on the day of surgery and more than 35 per cent required no postoperative analgesia, irrespective of the type and number of hernias repaired, similar to previous reports[4,7].

More than 10 per cent of patients with an apparent unilateral hernia were found at laparoscopy to have a significant and, in some cases, more pronounced defect on the other side. Others have found unsuspected contralateral pathology in up to 25 per cent of patients[8,9]. Bilateral repair was done under the same anaesthetic, helping to reduce the expense of further admissions. In long-term follow-up after unilateral Shouldice repair[10], 12 per cent of patients developed a contralateral hernia which required repair 3–8 years after the initial operation.

Speed of recovery and analgesic requirement after laparoscopic repair of bilateral hernias were the same as for unilateral hernias; no patient required overnight admission. In contrast, admission to hospital was common for synchronous open repair or alternatively sequential operation 3–5 weeks later was recommended[11].

Follow-up after open operation is usually reported at 6 weeks after surgery by which time many early complications will have resolved and may go unreported. Community-based studies[12] following open hernia repair have documented a complication rate of 28 per cent, up to four times the incidence of complications recorded in the hospital notes.

Although the follow-up is short, the recurrence rate in this series was less than 1 per cent and was similar to that reported previously[13]. Recurrences usually occur within 6 months of operation and are associated with some unrecognized technical problem at the time of surgery, such as rolling up of the mesh, inadequate fixation of the mesh in the region of Cooper's ligament or use of too small a mesh giving inadequate covering of the myopectineal area. The mesh is placed laparoscopically in the same position as in open operations such as those reported by Stoppa *et al.*[14] and Rignault[15]. Long-term results of laparoscopic repair might therefore be similar to those of these open methods.

The main disadvantage of laparoscopic repair is the requirement for general anaesthesia and, in the case of the transabdominal preperitoneal mesh repair, the need to cross the peritoneal cavity. The present results suggest that the operation can be performed successfully in more than 98 per cent of patients. The procedure has proved advantageous particularly for patients with bilateral and/or recurrent hernias and for those wishing to return rapidly to work, sporting activities or caring for dependent relatives[4].

Most patients under the age of 70 years, and some over, are suitable for day-case laparoscopic hernia repair. This reduces the demand for inpatient theatre time, inpatient beds and cost of nursing staff, and will help to meet the demands of the Patient's Charter[16].

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British Journal of Surgery 1996, 83, 1364–1366

General surgery with a special interest in vascular surgery: changing patterns of workload

M. S. WHITELEY, S. B. RAY-CHAUDHURI, J. CORNES, J. A. MICHAELS and R. B. GALLAND

Department of Surgery, Royal Berkshire Hospital, London Road, Reading RG1 5AN, UK
Correspondence to: Mr R B Galland

Prospective surveys of workload were carried out during 1989, 1990 and 1995. Analysis of outpatient referrals, inpatients and operations performed over periods of 3 months was undertaken and the changing patterns of general surgical and vascular surgical workload noted. The number of outpatient referrals rose throughout the study period because of a significant increase in the number of patients with both varicose veins and other vascular problems. There was an increase in the number of emergency admissions for vascular disease. The number of patients having general surgical operations fell; there was a corresponding increase in the number for arterial and venous disease. The general surgical component of a general surgical unit with a vascular interest is gradually declining, as increased numbers of patients with vascular problems are being referred and managed.

A survey from the Vascular Surgical Society of Great Britain and Ireland, published in 1992, suggested that only 4 per cent of members were pure vascular surgeons[1], the remainder carrying out a variable amount of general surgery. In Europe as a whole, specialization into vascular surgery is more advanced. Results of a questionnaire in 1988 suggested that in ten of 21 countries vascular surgery was a separate specialty. In the others it remained part of general or cardiothoracic surgery[2].

Patients with arterial disease take up disproportionate amounts of theatre time and inpatient beds compared with their general surgical counterparts[3]. Evidence is accumulating which suggests that increasing numbers of patients with vascular diseases are requiring treatment; it is now accepted that those with acute limb ischaemia are best managed on a vascular unit[4]. There is reluctance on the part of some general surgeons who do not carry out elective aortic aneurysm repair to deal with ruptured aneurysms. More patients may be referred for treatment as people become aware of the possibility of endovascular treatment. The authors have already experienced an increase in the number of patients with arterial disease referred by general practitioners and a corresponding increase in the number of procedures being performed[5,6]. These changes are taking place in the presence of decreasing resources.

The aim of this paper is to define the changing relationship between general surgery and vascular surgery in a district general hospital vascular unit.

Methods

The population of West Berkshire is approximately 450 000. General surgical cover is provided by six consultant surgeons. Before 1995, the department was split over two sites which were amalgamated during the summer of that year at the Royal Berkshire Hospital. Until December 1994 patients with retention of urine and haematuria were admitted to general surgeons; since then they have been admitted directly under the care of urologists.

The vascular unit was established in 1988. It is staffed by a consultant, house officer, shared senior house officer and shared registrar or senior registrar. In addition, staff grade surgeons carried out two waiting list initiative lists each week from 1991[7]. Vascular emergencies were usually admitted to the general surgical unit responsible for emergency admissions, with transfer to the vascular unit on the following day. There was a varicose vein clinic held at intervals of 2 weeks but other outpatient clinics contained a mixture of general and vascular cases, as referred by local general practitioners.

From 1988 to 1990 there was a steady increase in the number of vascular referrals and the number of vascular procedures performed[6]. Excluding varicose vein operations and major and minor amputations, 78 major vascular procedures were carried out in 1988, 114 in 1989 and 144 in 1990. Thereafter the annual number of operations reached a plateau, with a median of 138 (range 137–156) operations annually.

Detailed audits, each over a period of 3 months, were carried out in 1989[3], 1990 and 1995. Data were collected for the same 3-month periods for each year. Thus audits were performed during the time of an increasing vascular operative workload and at the start of, and 5 years into, a steady state. All new outpatient referrals were documented and were designated vascular, general surgical or varicose veins. Diagnoses were noted. Patients with conditions likely to be suitable for minor surgery, which could be carried out under local anaesthetic, were sent directly for operation on reviewing the referral letter. They are excluded from further analysis. Similarly, details were noted of all patients admitted to the unit, including in-hospital referrals and transfers. All operations carried out were also recorded.

Statistical analysis

Statistical comparisons throughout were made using χ^2 analysis and $P < 0{\cdot}05$ was considered significant.

Results

New outpatient referrals (Fig. 1)

The number of patients referred rose by approximately 56 per cent in 1995 compared with the previous two audits. There was an increase in the number with vascular problems noted throughout the study (1990 *versus* 1995: $\chi^2 = 11{\cdot}51$, 1 d.f., $P < 0{\cdot}001$). Similarly, the number of patients with varicose veins increased from 1989 to 1990 ($\chi^2 = 9{\cdot}69$, 1 d.f., $P < 0{\cdot}005$), and 1989 to 1995 ($\chi^2 = 14{\cdot}23$,

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Paper accepted 29 May 1996

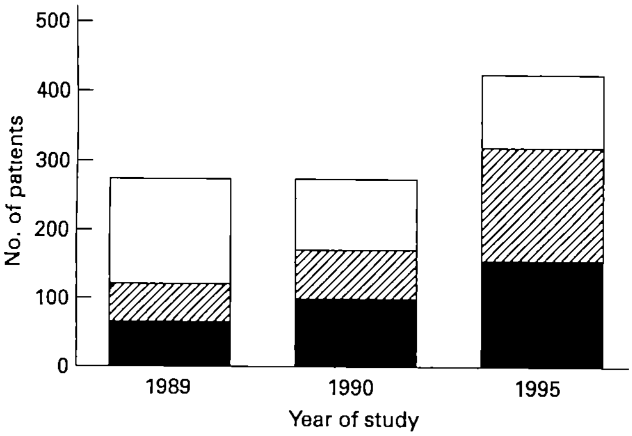

Fig. 1 Number of new outpatient referrals. ■, Varicose veins; ▨, vascular; ☐, general

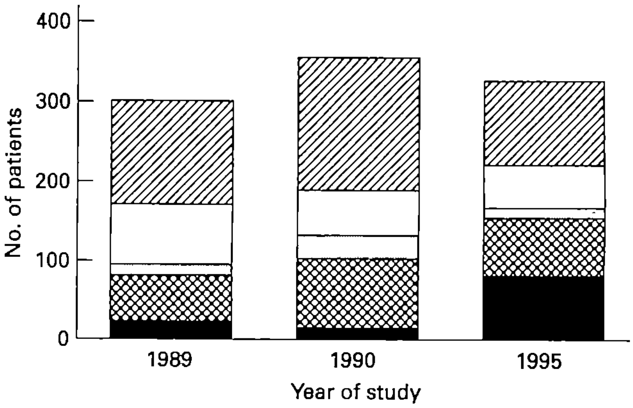

Fig. 2 Number of admissions to the ward. ■, Varicose veins; ▨, vascular elective, ☐, vascular emergency; ☐, general elective, ▩, general emergency

Table 1 Diagnosis at referral of new outpatients in 1989, 1990 and 1995

	1989	1990	1995
Vascular referrals			
Intermittent claudication	24 (44)	29 (41)	62 (37)
Rest pain, ulcer, gangrene, diabetic foot	18 (33)	17 (24)	27 (16)
Carotid disease	1 (2)	1 (1)	12 (7)
Aortic aneurysm	6 (11)	9 (13)	25 (15)
Venous disorder (excluding varicose veins)	1 (2)	2 (3)	16 (10)
Non-specific leg pain	2 (4)	4 (6)	12 (7)
Miscellaneous	2 (4)	8 (12)	13 (8)
Total	54	70	167
General referrals			
Anal pain or bleeding	34 (22)	27 (25)	22 (21)
Hernias	27 (17)	22 (20)	25 (24)
Breast disease	28 (18)	20 (19)	5 (5)
Lumps etc.	19 (12)	11 (10)	21 (20)
Abdominal pain or change in bowel habit	16 (10)	17 (16)	19 (18)
Miscellaneous	32 (21)	9 (8)	13 (12)
Total	156	106	105

Values in parentheses are percentages

1 d.f., $P<0{\cdot}001$). By contrast, the proportion of patients with general surgical conditions fell throughout the study (1989 *versus* 1990: $\chi^2=19{\cdot}37$, 1 d.f., $P<0{\cdot}001$); and 1990 *versus* 1995 ($\chi^2=15{\cdot}46$, 1 d.f., $P<0{\cdot}001$). Despite only one of six clinics being in an outlying hospital (Henley on Thames), 28 (27 per cent) of the 105 general surgical referrals came from that source.

The commonest vascular condition referred, after varicose veins, was intermittent claudication (*Table 1*). There was an increase in the number of patients referred with carotid disease and complex venous problems. The most obvious change in the general surgical referral diagnoses was the virtual disappearance of patients with breast disease.

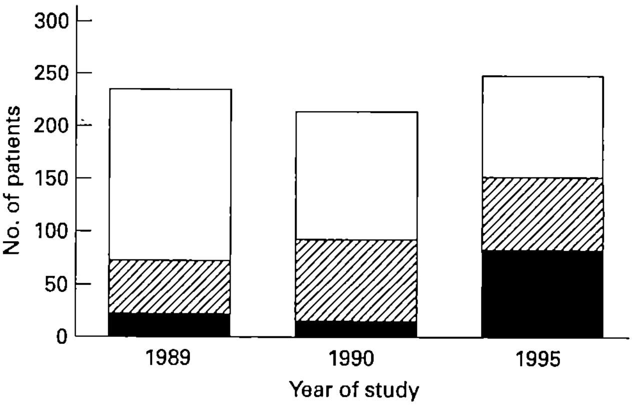

Fig. 3 Number of operations performed. ■, Varicose veins; ▨, vascular; ☐, general

Admissions (Fig. 2)

The total number of patients admitted to the unit did not differ significantly in each of the three audits. By 1995 there were fewer general surgical cases admitted and a greater number of patients with vascular disease. However, the only statistically significant changes involved the increased number of emergency admissions of patients with vascular disease between 1989 and 1990 ($\chi^2=4{\cdot}07$, 1 d.f., $P<0{\cdot}05$), and decreased emergency general surgical cases by 1995 ($\chi^2=15{\cdot}69$, 1 d.f., $P<0{\cdot}001$). The latter coincided with urological emergencies being admitted directly under the care of urologists. Following the introduction of the waiting list initiative in 1991, the number of patients admitted for varicose vein operations rose significantly by 1995 ($\chi^2=62{\cdot}87$, 1 d.f., $P<0{\cdot}001$).

Operations (Fig. 3)

The total number of operations carried out remained fairly constant throughout. The number of vascular operations increased between 1989 and 1990 ($\chi^2=12{\cdot}79$, 1 d.f., $P<0{\cdot}001$). There was a corresponding fall in the number of general surgical operations throughout the study (1989 *versus* 1990: $\chi^2=7{\cdot}42$, 1 d.f., $P<0{\cdot}01$); and 1990 *versus* 1995 ($\chi^2=14{\cdot}98$, 1 d.f., $P<0{\cdot}001$). The impact of the waiting list initiative is shown by an increase in varicose vein operations between 1990 and 1995 ($\chi^2=49{\cdot}00$, 1 d.f., $P<0{\cdot}001$).

The commonest vascular operation performed, after varicose vein surgery, was infrainguinal bypass (19 per cent of total), followed by abdominal aortic aneurysm repair (15 per cent). There was little change in type of operation throughout the three audits other than a reduction in the number of aortofemoral bifurcation grafts and rise in extra-anatomic revascularization for aortoiliac occlusive disease. Carotid endarterectomy became more frequent during the 1995 audit.

Discussion

Although the number of patients seen in the outpatient clinic increased during the study, there was little change in the number admitted to the unit or for operation. However, the proportion with vascular disease is increasing while that of patients with general surgical disease is decreasing. In general, greater resources are needed for an arterial case than for a general surgical case; the authors have shown previously that patients with arterial disease represented only about one-quarter of the caseload but accounted for almost half of the bed occupancy on the unit. Similarly, while arterial operations comprised only 20 per cent of the operating theatre caseload, they accounted for over 30 per cent of available operating time[3]. Others have emphasized the greater complexity of arterial cases compared with general surgical cases[8].

Some aspects of general surgery have been devolved to subspecialists. For example, few patients with breast disease are now referred to this unit; in Reading these patients are nearly all referred to a single surgeon with a special interest in breast disease. Similarly, the advent of laparoscopic surgery has resulted in the elective referral of patients with biliary disease largely disappearing. The appointment of general surgeons with a special interest in day-case surgery will further reduce the general surgical component of the authors' type of unit. The general surgical component has, in fact, largely been maintained by emergency cases, referrals through a general surgical clinic in an outlying hospital and general surgical problems developing in patients with vascular disease.

Organizing the management of vascular emergencies has been the subject of considerable recent debate[9–11]. It is unlikely that even in the largest district general hospital will there be sufficient numbers of surgeons with a vascular interest to maintain an independent vascular rota; adjacent hospitals may cooperate to establish such a rota. It is doubtful that this could be satisfactorily matched with existing general surgical emergency rotas and it seems inevitable that, in time, any vascular surgical emergency rota will separate completely from that dealing with general surgery.

It has been established that good results in vascular surgery are directly related to the number of operations an individual surgeon or institution carries out[12,13]. It has also been shown that those surgeons undertaking more arterial reconstructions achieve a lower rate of major amputation[14,15]. While the benefits to the patient seem clear, a recent survey on career intentions of surgeons in training revealed that few prospective vascular surgeons wanted a practice solely in vascular surgery. Most wished to retain some general surgery, although it was accepted that the majority of the workload would be vascular (M.S. Whiteley, unpublished results). Nevertheless, recent changes in training in the UK leave little doubt that future surgeons will not gain such broad experience as their predecessors did during their training period. Specialization in vascular surgery seems inevitable and this may well result in an increase in the number of pure vascular surgeons in the UK. The demise of 'general' surgery may occur in tandem; this was predicted some years ago[13]. The results of the present study suggest that this demise is not far off.

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British Journal of Surgery 1996, 83, 1367–1369

Changing patterns in aortoiliac reconstruction: a 7-year audit

M. S. WHITELEY, S. B. RAY-CHAUDHURI and R. B. GALLAND

Department of Surgery, Royal Berkshire Hospital, London Road, Reading RG1 5AN, UK
Correspondence to: Mr R. B. Galland

A prospective vascular audit was performed in this hospital between 1988 and 1994. There was a substantial increase in the number of vascular reconstructions (78 in 1988; 141 in 1994). Aortobifemoral grafts for occlusive disease comprised 18 per cent of the operations in 1988 and 0·7 per cent in 1994 (95 per cent confidence interval 0·086–0·259). There was a corresponding increase in the number of extra-anatomic grafts (from 3 to 20·6 per cent). There was a threefold increase in the number of percutaneous angioplasties performed for iliac occlusive lesions (14 in 1988; 41 plus 13 iliac stent procedures in 1994). This had no impact on the total rate of surgical intervention for aortoiliac disease, although it probably aided the shift to extra-anatomic reconstruction by dilatation of the donor side. To investigate whether this change is national, rather than local, graft sales figures were obtained from two vascular graft companies; these confirmed a national trend away from aortobifemoral grafting and provide some evidence to support an increase in extra-anatomic bypass grafting.

Aortoiliac occlusive disease requiring intervention can be treated by percutaneous angioplasty or reconstruction. The number of patients who present with vascular disease has increased significantly during recent years[1,2]. A study from Oxford[3] reviewed changes in treatment of aortoiliac disease over 4 years from 1985 to 1988. There was a doubling of the number of patients with aortoiliac disease who required intervention and a large increase in the number of percutaneous angioplasties of the iliac arteries (two in 1985; 34 in 1987). This was associated with a decrease in the proportion of patients having aortobifemoral bypass. There was no change in the proportion of patients who had extra-anatomic bypass grafting.

In 1988 a prospective audit was started to collect data relating to vascular reconstructions performed in this hospital. This database was analysed for a 7-year interval from 1988 to 1994 to define changes in the management of aortoiliac occlusive disease.

Patients and methods

The Royal Berkshire Hospital in Reading serves a population of approximately 460 000. A prospective audit of all vascular reconstructions performed under the care of one general surgeon with a vascular interest was started on 1 January 1988. During this audit the major indication for aortoiliac reconstruction was critical limb ischaemia. Unfortunately the audit did not identify preoperative risk factors but the general impression was of an increasingly elderly and high-risk population.

Numbers of reconstructions for aortoiliac occlusive disease were obtained and displayed as a percentage of the total number of vascular reconstructions performed in that year.

The number of percutaneous angioplasties of the iliac arteries was noted, as was the number of iliac stent procedures. Indications for stent placement included long iliac artery occlusion, asymmetrical stenosis that persisted despite balloon dilatation and bilateral stenosis of common iliac artery origin (requiring 'kissing stents').

In an attempt to identify whether the changes in this hospital were reflected throughout the UK, five companies that manufacture and sell vascular grafts were asked to provide data on any changes in sales of different vascular grafts Two companies responded (Vascutek, Inchinnan, UK; Bard, Crawley, UK). Proportions of each type of graft were calculated from the total number of grafts sold that year and were expressed as percentages. Company figures divided grafts into three categories: bifurcate (aortobifurcated grafts), straight (of any length) and externally reinforced grafts.

Statistical analysis of results was performed using 95 per cent confidence intervals, calculated with the Clintest statistical computer package (Clinical Statistics System version 1.01. Clinical Statistics 1993, UK).

Results

Aortobifemoral grafts

During the first 3 years of the study the proportion of aortobifemoral grafts was constant at about 20 per cent, despite an almost doubling of the vascular workload (from 78 to 144 cases) (*Fig. 1* and *Table 1*). Over the next 4 years there was a steady decrease in the proportion of aortobifemoral grafts. Reductions to 6·5 per cent in 1992 (95 per cent confidence interval (c.i.) 0·020–0·209), 3·6 per cent in 1993 (95 per cent c.i. 0·052–0·234) and 0·7 per cent in 1994 (95 per cent c.i. 0·086–0·259) were all statistically significant.

Extra-anatomic grafts

The extra-anatomic grafts used were predominantly axillobifemoral and femorofemoral grafts. In 1991 there

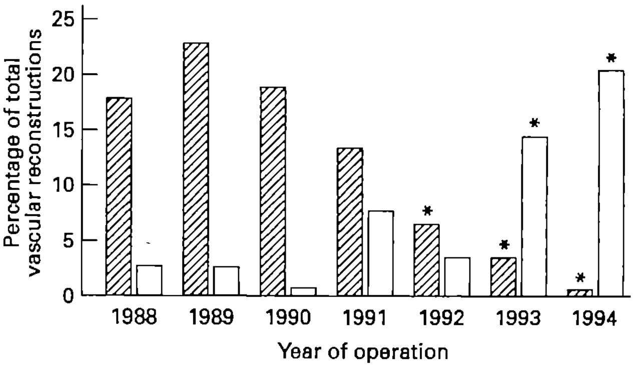

Fig. 1 Histogram showing vascular reconstructions for aortoiliac occlusive disease as a percentage of total vascular reconstructions. ▨, Aortobifemoral grafts; □, extra-anatomic grafts. *Significant change from 1988 level (95 per cent confidence interval)

Paper accepted 18 June 1996

Table 1 Number of aortobifemoral grafts, extra-anatomic grafts and total reconstructions by year

	Year						
	1988	1989	1990	1991	1992	1993	1994
Aortobifemoral graft	14	26	27	21	9	5	1
Extra-anatomic graft	2	3	1	12	5	20	29
Total reconstruction	78	114	144	156	139	137	141

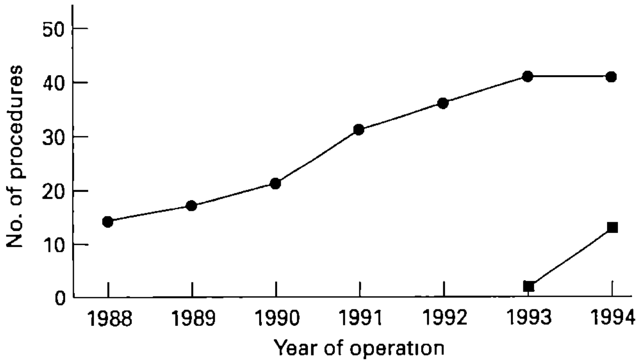

Fig. 2 Number of iliac artery angioplasties (●) and iliac stent procedures (■) from 1988 to 1994

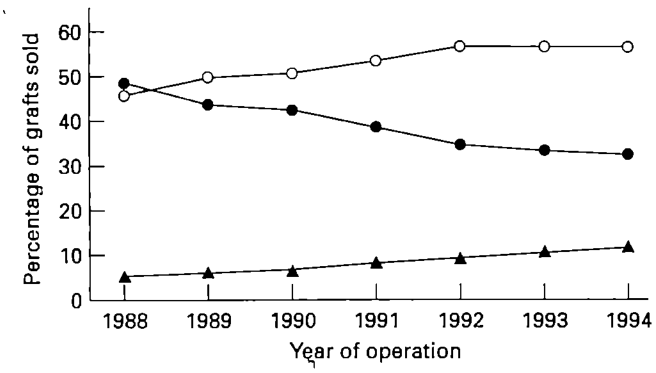

Fig. 3 Trends of graft sales nationally from 1988 to 1994. ●, Bifurcated aortic grafts, ○, straight peripheral grafts; ▲, externally reinforced peripheral grafts

was an increase in the proportion of patients having extra-anatomic grafts to 7·7 per cent but this was not significant (95 per cent c.i. −0·106 to 0·003). This increase mirrored the decrease in aortobifemoral grafts used in the same year (*Fig. 1*). In 1993 and 1994 there were significant increases in the proportion of extra-anatomic grafts used, 14·6 per cent (95 per cent c.i. −0·189 to −0·052) and 20·6 per cent (95 per cent c.i. −0·255 to −0·105) respectively.

Percutaneous angioplasty and iliac stents

The number of percutaneous iliac angioplasties performed rose steadily throughout the years studied from 14 in 1988 to 41 in 1994 (*Fig 2*). Iliac stent procedures were introduced in 1993; 13 were performed in 1994.

Graft manufacturer sales of vascular grafts

Throughout the 7 years studied the proportion of bifurcated aortic grafts sold steadily decreased. This was matched by a steady rise in sales of both straight and externally supported grafts (*Fig. 3*).

Discussion

Aortobifemoral grafting for occlusive vascular disease is very effective[4]. However, it is a major procedure with a mortality rate of approximately 6 per cent and a correspondingly high morbidity rate[5]. Extra-anatomic grafting has a similar mortality rate and lower morbidity rate despite being performed in older and less fit patients[6].

Analysis of operative procedures in this study showed a dramatic decrease in the number of aortobifemoral grafts from 1991 onwards with an increase in extra-anatomic grafts. Femorofemoral crossover grafting for unilateral iliac artery occlusive disease has excellent patency rates (92 per cent cumulative patency at 6 years) with a low early mortality rate (1·3 per cent) and short hospital stay[7]. Even less enthusiastic surgeons agree that femorofemoral grafts provide adequate function and limb salvage in patients who are at high risk or with limb-threatening ischaemia[4]. In the presence of bilateral iliac artery occlusive disease with a localized stenosis in one iliac artery, angioplasty on this side followed by femorofemoral crossover grafting produces acceptable results for limb salvage[8].

Axillobifemoral bypass grafting, once reserved for infected aortic grafts or patients with a 'hostile abdomen', has become an accepted alternative for-bilateral iliac occlusive disease. Primary patency rates of 78 per cent at 5 years have been reported, which are similar to those of aortofemoral bypass surgery[6,9].

The success of percutaneous angioplasty for iliac stenosis and short occlusions has been well documented[10]. Angioplasty combined with endoluminal stenting is used in an attempt to maintain patency in occlusion and recurrent stenosis[11]. However, careful analysis and follow-up of patients undergoing iliac angioplasty reveal 3-year patency rates below those expected from surgical reconstruction[12]. In the presence of critical ischaemia it has been suggested that surgical revascularization or combined angioplasty and operation could be a better option than angioplasty alone[13].

Previous studies from Leicester[1] and Edinburgh[14] have shown that large increases in the number of percutaneous angioplasties carried out make no difference to the number of vascular reconstructions performed. However, the present data have shown a trend away from aortobifemoral grafting towards extra-anatomic grafting. This is facilitated in some patients by dilatation of an iliac stenosis in a donor limb before femorofemoral crossover. Hence percutaneous angioplasty has influenced a changing pattern of reconstruction if not actually decreasing the number required.

Evidence was sought to suggest that this trend may be being repeated nationally. The proportion of different types of graft sold tends to confirm this. The number of bifurcated graft sold has dropped considerably, although these grafts are also used for aneurysm repair. Unfortunately there is no breakdown of what the grafts were used for. Clearly some of the straight grafts could be used for femoropopliteal or other reconstructions. The increased use of straight grafts with a significant decrease in the proportion of bifurcated grafts provides some evidence that there is a national trend away from aortobifemoral bypass grafts.

Acknowledgements

The authors thank Jennifer Carlyle from Vascutek Ltd and Sheridan Kumm from Bard Ltd for assistance in data collection.

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British Journal of Surgery 1996, 83, 1370–1372

Prospective study of carotid endarterectomy and contralateral carotid occlusion

A. F. DA SILVA, P. McCOLLUM, T. SZYMANSKA and L. DE COSSART

Audit Committee of the Vascular Surgical Society of Great Britain and Ireland, Department of Surgery, Countess of Chester Hospital, Liverpool Road, Chester CH2 1BQ, UK

Correspondence to: Mr A. F. da Silva

A total of 700 patients who had carotid endarterectomy (CEA) in the UK and Ireland during a 6-month interval between March and August 1994 were studied prospectively. Some 108 patients (15·4 per cent) had a contralateral internal carotid artery occlusion. Previous reports have shown an associated stroke rate of about 10 per cent in these patients. This study assessed complications and outcome for patients undergoing CEA with contralateral internal carotid artery occlusion compared with those without. The indications for surgery were comparable between the two groups although the patients with occlusion had a slightly higher incidence of arrhythmia and stroke. Intraoperative shunts were used in a significantly higher proportion of those with occlusion (83·3 *versus* 64·7 per cent, $P = 0·0001$). The combined death and stroke rate for patients with occlusion was 5·6 per cent compared with 2·4 per cent for the remainder (P not significant). On the basis of the present data, CEA with a contralateral carotid artery occlusion carries only a slight increase in the rate of postoperative stroke and death. This increase was not statistically significant and is lower than that reported previously.

The benefits of carotid endarterectomy (CEA) for symptomatic patients with carotid stenosis greater than 70 per cent are now accepted[1,2]. CEA in patients with contralateral carotid artery occlusion carries a higher peroperative and postoperative risk of stroke[3,4]. Improved results might follow if this high-risk group of patients could be identified and adequate measures instituted to overcome inadequate cerebral blood flow, such as obligatory intraoperative use of a shunt. The objectives of this prospective study were to assess the early outcome and complication rate of CEA in patients with a contralateral internal carotid artery occlusion and compare them with those of patients with no contralateral occlusion.

Patients and methods

A prospective study of CEA was designed in 1994 to examine 30-day outcome for all patients undergoing the procedure under 59 consultant surgeons. Sixty members of the Vascular Surgical Society of Great Britain and Ireland (VSS) were selected randomly to participate in the study. After the initial request for participation, six surgeons did not reply and a further group was recruited in order to obtain at least 500 patients for study. Actual participants represented approximately 50 per cent of known consultant vascular and general surgeons in the VSS who currently perform carotid surgery. A cross-section of surgeons was taken to include university centres, district general hospitals, full-time vascular surgeons and general surgeons with a vascular interest. Participation was entirely voluntary and surgeons were asked to include all patients undergoing carotid endarterectomy within a 6-month period from 1 March 1994 to 31 August 1994.

Although some 28 questions were asked, the main endpoints were death and postoperative stroke at 30 days. Individual pro formas were completed for each patient. No patient-identifiable data were recorded although the centre number was recorded initially until data verification was complete. Data were returned to the VSS office and entered into a customized database (DataEase; Sapphire Solutions, Ilford, UK). After preliminary analysis further specific requests were made for missing information and for details of patients where there appeared to be conflicting information. It was not possible to ensure that all cases were entered by the participating surgeon; however, 15 per cent of the total data was examined by an independent physician and neither extra strokes nor any further carotid endarterectomies were uncovered.

Comparison between discrete variables was made using the χ^2 test. The null hypothesis was rejected if $P < 0·05$ and P values shown are two tailed.

Results

There were 108 patients with contralateral internal carotid occlusion (15·4 per cent of the total series of 700). The male to female ratio was 2·7:1 in patients with an occluded artery compared with 2:1 in those without occlusion. Indications for surgery and risk factors for the two groups are summarized in *Tables 1* and *2*.

Consultant surgeons performed 78·7 per cent of operations in patients with occlusion compared with 80·6 per cent of procedures in those without. Mean hospital stay was 8·1 (range 2–39) days for the former patients compared with 6·9 (range 0–91) days in the latter. Mean operating time was 103·6 (range 20–240) min and mean carotid clamp time 11·2 (range 0–55) min in patients with occlusion. In those with a patent contralateral artery the respective values were 96·1 (range 10–240) min and 13 (range 0–85) min. Shunts were used in 83·3 per cent of patients with occlusion compared with 64·6 per cent of those without ($\chi^2 = 14·47$, 1 d.f., $P = 0·0001$, confidence interval 1·60–4·65). When no shunt was used, the mean clamp time was 28·6 (range 15–55) and 28 (range 1–85) min for patients with and without occlusion respectively. Intraoperative cerebral monitoring included electroencephalography, estimation of stump pressure or transcranial Doppler ultrasonography. Some 65·7 per cent of patients with occlusion had some form of peroperative cerebral monitoring compared with 64·4 per cent of those without occlusion. In patients with occlusion, stump pressure was measured in two of the 18 non-shunted patients compared with 12 of the 90 who had shunts. Completion assessment (such as palpation, continuous-wave Doppler imaging, duplex scanning, angiography or

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Presented to the Association of Surgeons in Glasgow, UK, May 1996

Paper accepted 19 June 1996

Table 1 Indication for operation

	Contralateral occlusion ($n = 108$)	No occlusion ($n = 592$)	P*
Amaurosis fugax	22 (20·4)	141 (23·8)	0·43
Transient ischaemic attack	29 (26·9)	222 (37·5)	0·03
Stroke	31 (28·7)	119 (20·1)	0·045
Asymptomatic stenosis	8 (7·4)	49 (8·3)	0·91
Contralateral symptoms	12 (11·1)	50 (8·4)	0·37
Vertebrobasilar symptoms	6 (5·6)	11 (1·9)	0·05

Values in parentheses are percentages. *χ^2 test

Table 2 Risk factors

	Contralateral occlusion ($n = 108$)	No occlusion ($n = 592$)	P†
Diabetes*	24 (22·2)	87 (14·7)	0·05
Ischaemic heart disease*	51 (47·2)	275 (46·5)	0·88
Hypertension*	58 (53·7)	315 (53·2)	0·92
Arrhythmia*	12 (11·1)	31 (5·2)	0·02
Mean (range) ipsilateral stenosis (%)	82 (50–99)	83 (30–99)	
Mean (range) contralateral stenosis (%)	100	44 (0–99)	

*Values in parentheses are percentages. †χ^2 test

Table 3 Complications and outcome

	Contralateral occlusion ($n = 108$)	No occlusion ($n = 592$)	P*
No complications	83 (76·9)	483 (81·6)	0·12
Single complication	20 (18·5)	95 (16·0)	0·57
Multiple complications	5 (4·6)	14 (2·4)	0·19
Transient ischaemic attack	0 (0)	16 (2·7)	
Stroke	4 (3·7)	11 (1·9)	0·40
Haematoma	5 (4·6)	27 (4·6)	0·99
Blow-outs	0 (0)	1 (0·2)	1.00
Neuropraxia	8 (7·4)	22 (3·7)	0·14
Contralateral symptoms	2 (1·9)	9 (1·5)	1·00
Cardiovascular complications	4 (3·7)	11 (1·9)	0·40
Other complications	8 (7·4)	32 (5·4)	0·43

Values in parentheses are percentages. *χ^2 test

Table 4 Outcome

	Contralateral occlusion ($n = 108$)	No occlusion ($n = 592$)
No. alive at 30 days	107 (99·1)	585 (98·8)
No. dead at 30 days	1 (0·9)	7 (1·2)
Cardiac death	0 (0)	4 (0·7)
Neurological death	0 (0)	3 (0·5)
No. fully recovered at 30 days	102 (94·4)	552 (93·2)
No. with disabling deficit	2 (1·9)	10 (1·7)
No. with non-disabling deficit	3 (2·8)	23 (3·9)

Values in parentheses are percentages. P values for outcome between the two groups were not significant

Table 5 Outcome with shunt use in patients with contralateral carotid occlusion

	Shunted ($n = 90$)	No shunt ($n = 18$)
Overall complications	22	3
Death	0	1
Stroke	4	0

angioscopy) was done for 89·9 per cent of the patients with an occluded artery compared with 88·8 per cent of those without.

Complications and outcome for the two groups are shown in *Tables 3* and *4*. There were no significant differences in the operative complication rates. Postoperative outcome for the two groups was almost identical. In patients with an occluded contralateral carotid artery, a comparison was also made between the shunted *versus* non-shunted subgroups. The numbers are too small for statistical analysis but are displayed in *Table 5*.

Discussion

There is debate concerning the risk of CEA in the presence of a contralateral occlusion with reported peroperative stroke rate ranging from 3 per cent[5] to 10 per cent[3,4]. The present data disclosed that patients referred for CEA in the UK and Ireland had an overall rate of contralateral carotid occlusion of 15·4 per cent which is similar to reported rates of 15 per cent[6] and 13 per cent[7]. In this study those with occlusion had a significantly higher preoperative incidence of stroke (but not of transient ischaemic attack), and also a higher incidence of diabetes and cardiac arrhythmia which might have indicated a higher surgical risk. This risk was not borne out in the subsequent outcomes. Inadequate collateral blood flow is thought to be a predisposing factor for neurological complications in high-risk patients undergoing CEA. Routine carotid shunting should be highly effective and perhaps even obligatory[3] to overcome this[8]. However, shunt insertion is occasionally difficult and may increase the risk of stroke from emboli[8,9]. This was apparently a view not shared by the surgeons in this study, where the use of shunts was significantly higher in patients with occlusion (83·3 *versus* 64·6 per cent). Although the operative complication rate was higher in patients with an occluded contralateral artery, the difference between the groups was not statistically significant. There was no statistical difference in the postoperative death rates. In terms of peroperative monitoring and completion assessment, the surgeons' practice did not differ between the two groups, suggesting that complication rates and outcome, in what is considered by some a high-risk group, were not affected by availability of peroperative monitoring resources.

A shortcoming of this study is that, to ensure maximum reporting compliance by participating surgeons, a relatively short period of audit was chosen which precludes long-term follow-up of these patients. This study represents the first prospective national survey in Great Britain and Ireland of CEA in patients with contralateral internal carotid occlusion and is valid in its assessment of immediate postoperative outcome. The conclusion from this study is reassuring. The risk for the patient with contralateral carotid occlusion is not significantly higher than that for a patient without occlusion and the continuing practice of CEA in the presence of a contralateral occlusion is therefore supported.

Acknowledgements

The authors gratefully acknowledge the contribution from the following surgeons who have taken part in this study: Mr D. Allen, Chichester, Mr A. Barros D'Sa, Belfast, Mr R. Baird, Bristol, Mr J. Beard, Sheffield, Professor P. Bell, Leicester, Mr C. Bishop, London, Mr S. Brearley, London, Professor K Burnand, London, Mr M. Calvert, Glasgow, Mr A. E. P. Cameron, Ipswich, Mr B. Campbell, Exeter, Mr A. D. B. Chant, Southampton, Mr D. Charlesworth, Manchester, Mr J. Chester, Taunton, Mr J. F. Clegg, Crewe, Mr J. Collin, Oxford, Mr R. E. C Collins, London, Mr S. Darke, Bournemouth, Mr C. P. Gibbons, Swansea, Mr M. Gough, Leeds, Mr R. P. Grimley, Stourbridge, Mr A. J. Guy, Leighton, Ms L. Hands, Oxford, Mr P. Harris, Liverpool, Mr R. Hughes, Burnley, Mr A. P Jayatunga, Wordsley, Mr N. Jones, Newcastle upon Tyne, Mr J. Kelly, Lancaster, Mr O. E. Klimach, Rhyl, Mr D. Lambert, Newcastle upon Tyne, Mr P. Lamont, Bristol, Mr R. Lane, Winchester, Mr P. Lear, Bristol, Mr S. Leveson, York, Mr N. London, Leicester, Mr A. J. McIrvine, London, Professor A. Mansfield, London, Professor C. McCollum, Manchester, Mr P. McCollum, Dundee, Mr J. McCormick, Dumfries, Mr S. McPherson, Leicester, Professor P. Morris, Oxford, Mr R. Naylor, Leicester, Mr S. Parvin, Bournemouth, Mr D. Ratcliffe, Northampton, Professor V. Ruckley, Edinburgh, Professor G. Shanik, Dublin, Mr C. Shearman, Southampton, Mr M. Simms, Birmingham, Mr C. L. Strachan, Brighton, Mr P. Taylor, London, Mr J. Thompson, Exeter, Mr P. Vowden, Bingley, Mr M. Walker, Manchester, Mr J. H. H. Webster, Southampton, Mr G. Welch, Ayr, Mr D. Wilkins, Plymouth, Mr A. R. Wilkinson, Hull, Mr J. Wolfe, London

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British Journal of Surgery 1996, 83, 1373–1374

Short note

Carotid endarterectomy: an underutilized means of stroke prevention

C. D. IRVINE, A. H. DAVIES*,
P. M. LAMONT and R. N. BAIRD

*Department of Surgery, Vascular Studies Unit, Bristol Royal Infirmary, Bristol and *Department of Surgery, Charing Cross and Westminster Medical School, Charing Cross Hospital, London, UK*

Correspondence to Mr C D. Irvine, Department of Surgery, Vascular Studies Unit, Bristol Royal Infirmary, Bristol BS2 8HW, UK

The results of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) demonstrated that carotid endarterectomy (CEA) was beneficial in symptomatic patients with a stenosis of the internal carotid artery of more than 70 per cent[1,2]. There is evidence that general practitioners are unaware of these trial results[3], and that epidemiologists are reluctant to accept the benefits suggested by these studies[4]. Vascular surgeons feel that CEA should be purchased and performed[4], and that underperformance of CEA diminishes the potential of the operation as a means of stroke prevention.

In the UK and North America the stroke rate is similar[5]. In the UK in 1991 the estimated rate of CEA was 24 per million per year[6]. In the USA the rate was 15 times higher at 360 per million[6]. Epidemiological studies suggest that 160 patients per million have a greater than 70 per cent symptomatic internal carotid artery stenosis that is amenable to surgery. This figure is derived from an incidence of first transient ischaemic attack (TIA) of 600 (range 350–3000) per million population[5,7], 20 (range 6–30) per cent of patients with TIA having ipsilateral carotid artery disease amenable to surgery[8–11], and only one-half to two-thirds of patients fit for surgery[11,12]. This gives 80 patients with TIA per million population. There is a similar number of patients with non-disabling stroke[13], suggesting that 160 patients per million population might benefit from CEA. Other authors interpret the epidemiological data differently and suggest that this figure might be reduced by half[4] or one-third[11]. Any figure may be an underestimate as over 50 per cent of TIAs are not reported to general practitioners[7,14].

Paper accepted 22 April 1996

Methods and results

The number of CEAs performed in the years 1990–1993 and population data for the English health regions were supplied by the Department of Health from Hospital Episode Statistics. Similar data for the health boards of Scotland from 1990–1993 were supplied by the Information and Statistics Division of the National Health Service in Scotland. Northern Irish data for 1989–1994 were supplied by the Strategy and Intelligence Group of the Department of Health and Social Services.

England

The rates of CEA per million population for the 3 years from April 1990 to April 1993 are shown in *Table 1*. The number of CEAs increased over time. There are variations in the rates between health regions; for instance South West Thames had a rate of 11·5 CEAs per million population in 1992–1993 while Yorkshire had a rate of 67·5 CEAs per million population. The latter rate represents one-third of the number that might be predicted for its population base and one-sixth of those that might have been expected to be carried out in an equivalent setting in the USA.

Table 1 Annual numbers and rates of carotid endarterectomy in England, Scotland and Northern Ireland compared with predicted rates (from epidemiological data) and equivalent rates in the USA

Area	Years*					Predicted annual CEA rate	CEAs at USA rate
	1989–1990	1990–1991†	1991–1992‡	1992–1993§	1993–1994¶		
England (population 45 million)							
No of operations		584	1288	1563		7200	16 200
CEAs per million		13·0	28·6	34·7			
Scotland (population 5·1 million)							
No. of operations		72	143	285	323	820	1 850
CEAs per million		14·1	28·0	55·9	63·3		
Northern Ireland (population 2·1 million)							
No. of operations	57	30	41	14	57	335	760
CEAs per million	27·1	14·3	19·5	6·7	27·1		

For England, number of operations relates to 'estimated number of Finished Consultant Episodes' for OPCS4 (Office of Population Census and Surveys) codes L29.4 and 5, and L29.8 and 9 combined (Department of Health; latest available estimate 1995). The number of operations performed in Scotland is derived from 'discharges' rather than Finished Consultant Episodes for the same OPCS codes as England *English and Northern Irish data are for financial years; Scottish data are given for calendar years †1990, ‡1991, §1992 and ¶1993 CEA, carotid endarterectomy

Scotland

Table 1 illustrates the CEA rates for Scotland. The Scottish Health Boards also show wide variation in the rate of CEA with an increase over time. Three health boards, Ayrshire and Arran, Dumfries and Galloway, and Tayside had CEA rates of greater than 100 per million population in 1993; Tayside had a rate of 134·1 in that year. The average Scottish CEA rate was 63·4 per million in 1993.

Northern Ireland

CEA rates are shown in *Table 1*. The years 1989–1994 are financial years. The 'coverage of diagnosis figure' – an estimate of data completeness – for 1992–1993 is only 75 per cent which might explain the strikingly low rate of 14 CEAs per million in this year. The data for 1993–1994 are incomplete with 1 per cent of all data unavailable. These anomalies make comment on this information speculative.

Discussion

Reduction in the number of stroke victims would have marked implications on health care budgeting but to attempt to do this by using CEA would have a great effect on the provision of surgical services. The most recent figures (*Table 1*) show that the English CEA rate is less than 40 CEAs per million. This probably represents only one-third of the workload needed to provide the greatest impact on stroke and only one-sixth of that carried out in the USA.

While financial constraints in the National Health Service and financial incentives in the USA may affect CEA rates, TIA and stroke rates are remarkably similar in these countries[5]. It is unclear whether patients in the UK with carotid artery disease are not diagnosed, not investigated, not referred or simply not operated on. It may be that the results of the ECST and NASCET are not widely known by general practitioners[3], which would affect patient referral. Conversely, the yearly doubling of the Scottish CEA rate between 1990 and 1992 may reflect the impact of these studies on general practitioners.

The effect of the type of healthcare provision may be crucial. The Australian CEA rate for the public hospital system in 1993 and 1994 was 210 per million population (M. Appleberg, personal communication), while the Swedish rate in 1994 was 58 per million population[15].

Data reliability is important. The accuracy of the Scottish morbidity data for abdominal aortic aneurysm has recently been called into question[16]. The incomplete Northern Irish data detected by 'coverage of diagnosis' analysis has been described. The Department of Health figures for England are 'grossed' to compensate for missing data; valid diagnostic coverage is greater than 80 per cent. The Information and Statistics Division of the National Health Service in Scotland reports no data deficiencies.

If attitudes change in the UK, market forces may require an increased provision of surgical intervention. This should be welcomed, but the potential scale of the demand is worrying. To perform an equivalent of half of the CEAs currently carried out in the USA, each British surgeon would need to perform between five and six times more CEAs than at present.

Acknowledgements

The authors thank Ms A. Babalola (Department of Health, England), Mr S. McCann and Mr O Johnston (Department of Health and Social Services, Northern Ireland), and Mr J. Moran (Information and Statistics Division, National Health Service, Scotland). C. I is supported by the Stroke Association.

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British Journal of Surgery 1996, **83**, 1375–1379

Vein morphology and bypass graft stenosis

K. VARTY, K. PORTER, P. R. F. BELL and N. J. M. LONDON

Department of Surgery, University of Leicester, Clinical Sciences Building, Leicester Royal Infirmary, Leicester LE2 7LX, UK
Correspondence to: Mr K. Varty

Vein wall morphology (intimal and medial thickness) was studied in a consecutive series of 100 veins before organ culture. The development of a proliferative neointima after 14 days in culture was quantified by measuring neointimal thickness, and the relationship between this and the original vein wall morphology was investigated. The correlation between the intimal or medial thickness before culture and neointimal thickness following culture was poor (r_S intima/neointima = 0·21, r_S media/neointima = 0·09). Long saphenous vein biopsies were obtained from 53 patients at the time of infrainguinal bypass surgery and their morphology was studied as above. Median intimal and medial thickness before grafting was 21 (range 2–208) and 245 (range 108–557) μm respectively. After 12 months in a colour duplex graft surveillance programme, 46 grafts were patent and 17 of these had developed a stenosis. There was no difference in intimal (28 *versus* 19 μm, $P = 0·1$) or medial (247 *versus* 245 μm, $P = 0·47$) thickness between stenosed and non-stenosed grafts respectively. Both the laboratory and clinical evidence from this study fail to support the hypothesis that pre-existing vein wall thickening is a key factor in the aetiology of vein graft stenosis.

Vein remains the conduit of choice for lower-limb arterial bypass grafts, the ipsilateral long saphenous vein being the usual and most convenient source. However, in many patients undergoing coronary and peripheral artery bypass the long saphenous vein has been shown to be abnormal or diseased on microscopic examination[1–5]. Panetta and colleagues[6] have demonstrated at the macroscopic level that palpably thickened, varicosed, calcified or recanalized veins have a poor patency rate compared with 'normal' veins (30-month patency 32 *versus* 73 per cent). These findings are not perhaps surprising and it is now widely accepted that vein that is of 'poor quality' on gross inspection at the time of surgery should probably be excised and replaced with vein from an alternative source. Further evidence has emerged, however, suggesting that even microscopic changes in wall morphology may influence graft performance[7,8]. This has potentially greater implications for surgical practice since the detection of these more subtle changes in the vein at the time of grafting is difficult and largely beyond current surgical technique or technology[9]. These veins appear to be perfectly normal on physical inspection and eminently suitable for use as a graft[7]. Before adopting techniques such as intraoperative vein biopsy[7], vein wall compliance measurement[8] or intravascular ultrasonography[10] in an attempt to detect this subclinical vein wall thickening, further evaluation of the importance of this variable on clinical graft outcome seems warranted. The aim of this study, therefore, was to analyse the correlation between long saphenous vein morphology and the process of intimal hyperplasia leading to graft stenosis.

Patients and methods

Histological analysis

The techniques used to collect, transport and process samples of long saphenous vein for histological analysis have been described previously[11]. In brief, minimal handling of the vein occurred during surgery, and the vein biopsy was taken before preparation for grafting and placed immediately in calcium-free Krebs–Ringer solution to counteract spasm. Fixation was always performed under tension by opening the vein longitudinally and pinning it on to a resin gel base with the luminal surface uppermost. During this process the vein wall can be stretched out to maximum length at which point there is strong resistance to further stretch. The reproducibility of this technique has been validated previously[11]. Formal saline (10 per cent) was used for overnight fixation followed by embedding in paraffin wax. Transverse sections of the vein were stained with Millers elastin and monoclonal smooth muscle actin. All measurements were performed by two independent observers taking the mean of 30 values per section using a computerized image analysis system (Improvision, Canley, UK). All vein sections were coded so that the observers did not know from which patient the section had originated, thereby preventing any bias.

In vitro *intimal hyperplasia*

During organ culture, the long saphenous vein develops a cellular neointima with several of the features of intimal hyperplasia seen in retrieved stenosed vein grafts[12]. This *in vitro* model of intimal hyperplasia has been established in the authors' laboratories[13]. For each vein put into culture a control segment of uncultured vein is fixed under tension to provide a histological baseline. To study the influence of pre-existing vein wall histological abnormalities on the development of intimal hyperplasia in culture, intimal and medial thicknesses were measured in a consecutive series of 100 veins before culture, and correlated with neointimal thickness after 14 days. The intima was defined as the layer of vein wall between the endothelium and the internal elastic lamina, the media as the layer between the internal elastic lamina and the adventitia, and the neointima as the cellular layer developing in culture beneath the endothelium but superficial to the original intima. All veins were retrieved from patients undergoing arterial surgery for either coronary or peripheral bypass grafting or carotid endarterectomy where vein was used as a patch.

Clinical graft stenosis

In this prospective study, samples of long saphenous vein were taken from 53 patients undergoing lower-limb vein bypass grafts and analysed as above. The biopsy was always taken from the distal long saphenous vein just beyond the segment used for the actual graft. Previous studies[8] and the authors' own observations have suggested an increased incidence of intimal changes in the distal long saphenous vein. When a section of 'poor-quality' vein was excised during surgery, this was not used for histology since

Paper accepted 29 May 1996

it was unlikely to be representative of the remainder of the graft. Some mildly varicosed veins were used as grafts during the period of the research, but these were not included in the study. The aim was to restrict this enquiry to veins that were judged at the time of surgery by visual inspection and palpation to be normal and suitable for the purpose of bypass grafting.

Three patients had grafts that failed within 30 days and were excluded from the study. The remaining 50 patients (37 men and 13 women of median age 71 years) entered a colour duplex graft surveillance programme for the detection of graft stenosis[14]. Three grafts failed and one patient died in the first 3 months, leaving 46 grafts which completed follow-up to a minimum of 12 (median 12, range 12–31) months. Two of the failed grafts occurred in diabetic patients with limited run-off but the cause of failure in the third graft was unknown. There were 28 femorocrural, 16 femoropopliteal below-knee and two femoropopliteal above-knee grafts; all were inserted for critical limb ischaemia apart from two for claudication and three for popliteal aneurysm. Six of the grafts were composite, a section of 'poor-quality' long saphenous vein being excised and replaced with arm vein. At the completion of the study the relationship between the histological features before insertion of the graft and the incidence of graft stenosis was analysed.

Statistical analysis

The correlation between vein wall thickness and neointimal thickness in culture was analysed using Spearman's rank correlation (r_S). The association between graft stenosis and vein wall thickness was analysed with the Mann–Whitney *U* test.

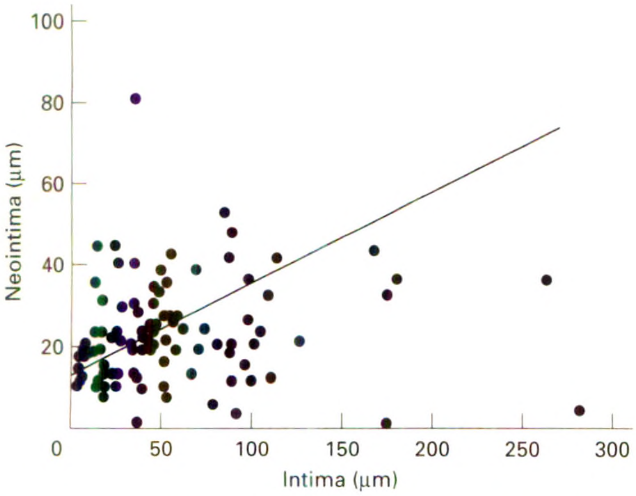

Fig. 1 Scatterplot of intimal thickness in the vein before culture and neointimal thickness after 14 days in culture. ($r_S = 0{\cdot}21$)

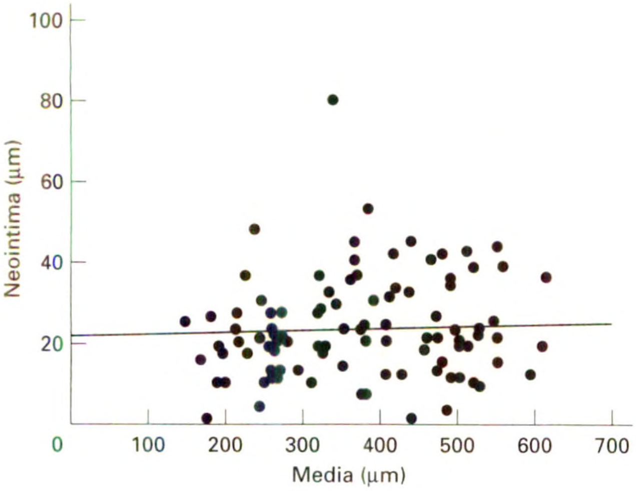

Fig. 2 Scatterplot of medial thickness in the vein before culture and neointimal thickness after 14 days in culture. ($r_S = 0{\cdot}09$)

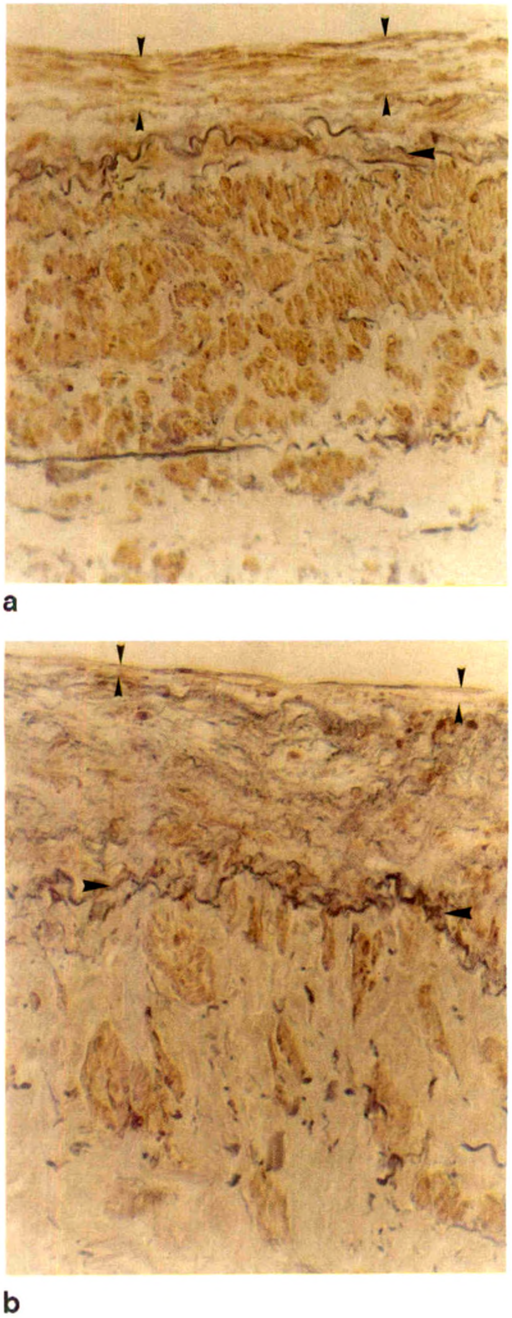

Fig. 3 Transverse sections of vein. **a** Internal elastic lamina (large arrowhead) separating thin intima (12 µm) from media. A neointima (between small arrowheads) consisting of several layers of actin-positive cells has developed in culture, with a thickness of 25 µm. **b** Internal elastic lamina (large arrowhead) delineating a thickened intima (74 µm). Above this a thin neointima (small arrowheads) has formed in culture, less than 10 µm thick. (Smooth muscle actin and Miller's elastin stain, original magnification ×160)

Results

In vitro *intimal hyperplasia*

There was no demonstrable correlation between intimal or medial thickness and the development of neointimal hyperplasia in culture: r_S intima/neointima = 0·21; r_S media/neointima = 0·09 (*Figs. 1* and *2*). No correlation was found between intimal and medial thickness ($r_S = 0·1$) in these veins and the combination of intima plus media also failed to show any relationship to neointimal thickness ($r_S = 0·14$). There were, therefore, a number of veins with no major histological abnormalities before culture which developed a thick neointima in culture (*Fig. 3a*) and a number of veins that were clearly abnormal before culture but which failed to develop a significant neointima in culture (*Fig. 3b*). While this diversity between veins in their propensity to develop neointimal hyperplasia in culture is interesting, it does not appear to be due to pre-existing histological changes in the vein wall.

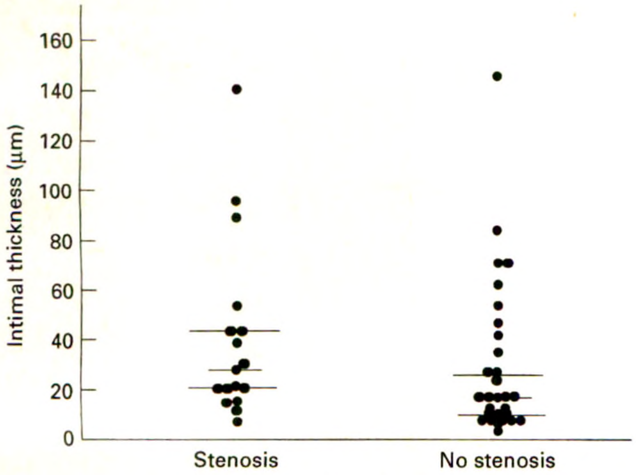

Fig. 4 Comparison of intimal thickness between grafts that did and did not stenose. Wide and narrower bars represent median and 95 per cent confidence interval (c.i.) respectively. There was no difference in intimal thickness between stenosed (median 28 µm) and non-stenosed (19 µm) grafts (95 per cent c.i. − 1·5–22; $P = 0·1$, Mann–Whitney *U* test)

Clinical graft stenosis

Seventeen of 46 grafts developed a stenosis, 13 in the graft body and four at the distal graft anastomosis. Two of the six composite grafts developed borderline stenosis at the venovenostomy which were not treated but closely monitored. These lesions were not included in the data as true graft stenoses. No other lesions developed in the composite grafts. Median time for the detection of a stenosis was 6 (range 2–17) months. Median intimal thickness of the vein before grafting was 21 (range 2–208) µm. The corresponding figure for medial thickness was 245 (range 108–557) µm. There was no difference in intimal thickness between vein grafts that subsequently developed stenosis and those that did not (median 28 *versus* 19 µm, 95 per cent confidence interval (c.i.) −1·5–22, $P = 0·1$) (*Fig. 4*). There were grafts that

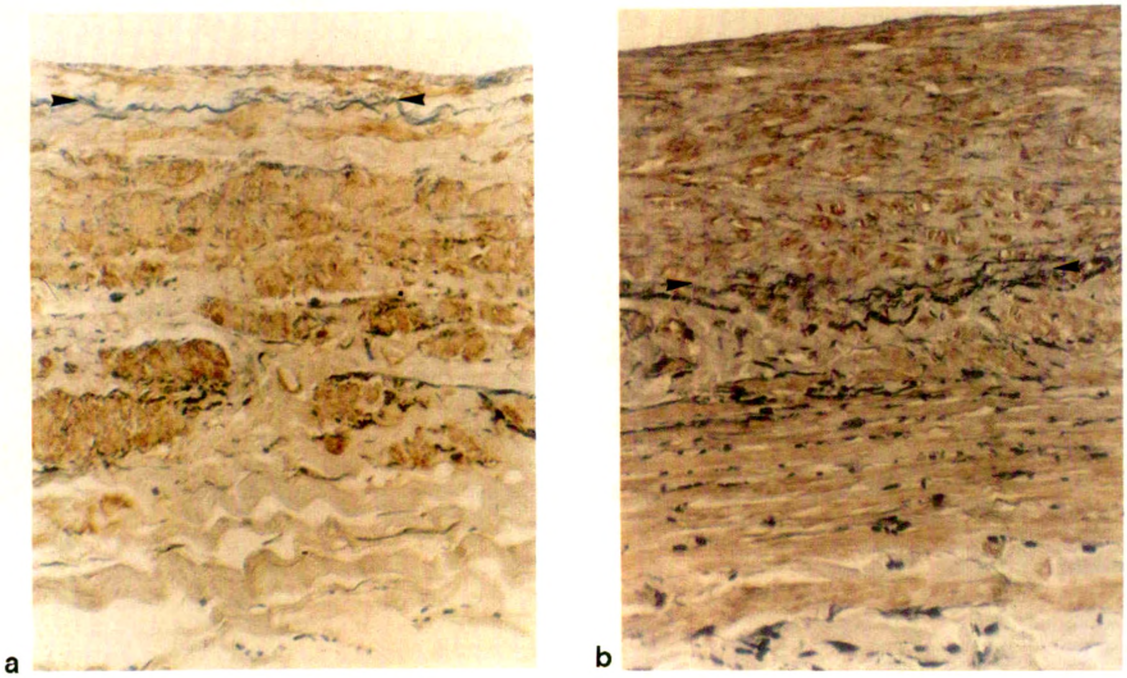

Fig. 5 Transverse sections of vein. **a** Internal elastic lamina (between arrowheads) separating thin intima (11 µm) from medial muscle bundles and adventitia (bottom of figure). This relatively normal long saphenous vein developed a graft stenosis. **b** Internal elastic lamina (between arrowheads) separating thickened intima (95 µm) from circular medial smooth muscle layer (108 µm). Despite this pre-existing abnormality the vein performed well as a graft without stenosis. (Smooth muscle actin and Miller's elastin stain, original magnification × 160)

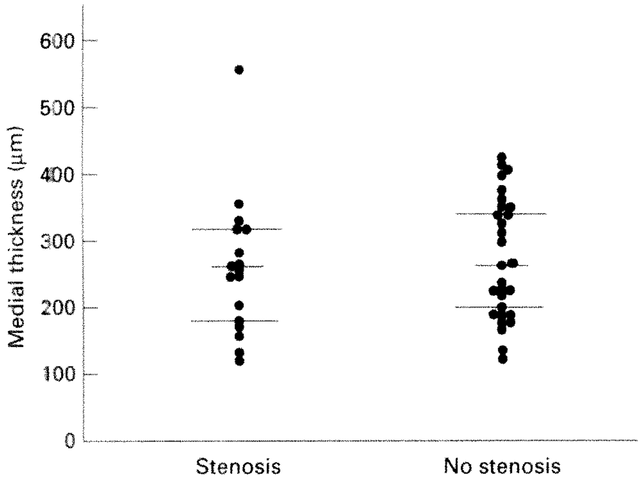

Fig. 6 Comparison of medial thickness between grafts that did and did not stenose. Wide and narrower bars indicate median and 95 per cent confidence interval (c.i.) respectively. There was no difference in medial thickness between stenosed (median 247 μm) and non-stenosed (245 μm) grafts (95 per cent c.i. −62–40; $P = 0{\cdot}47$, Mann–Whitney *U* test)

originally had no major histological abnormalities which went on to stenose (*Fig. 5a*) and, conversely, grafts with marked intimal thickening in the original vein which did not stenose (*Fig. 5b*). Similarly, there were no significant differences in medial dimensions between grafts that stenosed and those that did not (median 247 *versus* 245 μm, 95 per cent c.i. −62–40, $P = 0{\cdot}47$) (*Fig. 6*). A combined intimal plus medial thickness measurement was computed for each vein but no relationship between this and graft stenosis was apparent ($P = 0{\cdot}64$). Reanalysis of all the data based on true intragraft stenoses alone, excluding the anastomotic lesions, produced similar results.

Three grafts that failed during surveillance were excluded from the study since the precise cause of failure was unknown and no graft stenosis had been shown on duplex scanning. The intimal thickness in these veins was 6, 25 and 139 μm respectively. Inclusion of these figures in the above analysis as grafts that did not stenose again did not alter the statistical result of the study.

Discussion

The wide variation in the morphology of the human long saphenous vein in patients undergoing arterial surgery is confirmed in this study. In particular, veins used for bypass grafting that were selected as macroscopically 'normal' during surgery proved still to be very variable in microscopic structure. Although angioscopy can be used to screen for gross vein abnormalities such as webs, calcification, thrombus and retained valve cusps[9,15], its ability to detect more subtle abnormalities, such as intimal thickening, is limited[9]. It is clear, therefore, that with current surgical techniques many veins with a thickened cellular intima are being used as bypass grafts. The important question is whether this is of detriment to the success of the bypass procedure.

Marin and colleagues[7] studied microscopic abnormalities in vein biopsies taken at the time of surgery and fixed under distension of 100 mmHg. They found that intimomedial thickening and cellularity were strongly associated with failed or failing grafts at 18–30 months. Davies and co-workers[8] have also demonstrated a link between veins of poor compliance, usually due to high-grade intimal hyperplasia, and subsequent graft stenosis. In contrast to these findings, Leu and colleagues[16], studying the morphology of 318 human long saphenous veins, concluded that 'phlebosclerosis' was common in autologous vein grafts and of little consequence for the survival of the graft. Cheanvechai and colleagues[1] also described phlebosclerosis in 27 per cent of long saphenous veins used for coronary artery bypass grafting. At follow-up angiography the patency rates were almost identical for grafts from normal (87·9 per cent) or phlebosclerotic (89·5 per cent) veins. There is, therefore, some disagreement in the published literature regarding the significance of long saphenous vein morphology in relation to graft survival, although the more recent evidence[7,8] has strengthened the argument that there is a link.

The *in vitro* data from the present study reveal no correlation between intimal or medial thickness and the development of a neointima in organ culture. This lends no support to the hypothesis that veins with a thickened intima might have an additional proliferative potential for forming a neointima above that of 'normal' vein with a thin intima. In keeping with this, the clinical study of infrainguinal vein bypass grafts failed to demonstrate any clear association between pre-existing intimal or medial thickening and subsequent graft stenosis. Although a small increase in intimal thickness was noted in the group with stenosis (28 *versus* 19 μm), the limited clinical significance of this is shown in *Fig. 4*. The wide variation in intimal thickness produces a large overlap between the stenotic and non-stenotic groups. In practice, therefore, a single measurement of intimal thickness taken from a vein biopsy at the time of surgery would be a poor predictor of subsequent graft performance. Although in a larger study a statistical rejection of the null hypothesis might possibly emerge (type II error), the lack of clear separation between stenotic and non-stenotic grafts would remain. Vein morphology by present methods, therefore, is unlikely ever to be a clinically useful indicator of the risk of graft stenosis. Although wide, the 95 per cent confidence intervals constructed for the sample of veins in this study support the null hypothesis that there is no difference in intimal thickness between grafts that subsequently stenose and those that do not.

These *in vivo* results differ from those of the previous studies by Marin *et al.*[7] and Davies and colleagues[8]. Part of the explanation for these contrasting findings may lie in the different methods used for assessing vein wall morphology in the three studies. Although Marin *et al.* measured intimal thickness, the actual anatomical landmarks used to define this are unclear. The present authors have found that a specific elastin and smooth muscle stain is often necessary to delineate the internal elastic lamina, which defines the extent of the intima. Using a different staining technique, Marin and colleagues quoted values of 'intimal thickness' approximately tenfold greater than those in the present study; these actually refer to a combined intima plus inner media measurement. A measurement of intima plus media in the present study also failed to predict graft stenosis. Davies and colleagues[8] used a semiquantitative, subjective, grading system to categorize intimal thickening and, again, it is difficult to correlate these grades with the thickness measurements made under tension in the present study. The three studies, although similarly concerned with the link between vein morphology and graft outcome, have used different measurements and so are not directly comparable. A further issue is the focal nature of some of the changes seen in the long saphenous vein. A single biopsy from the vein may miss features present at other levels. This factor could explain the lack of correlation between biopsy features and graft stenosis in the present study, but it makes the good correlation found in the studies of Marin *et al.* and Davies and co-workers surprising.

The other unknown variable between these three studies is the selection of patients for surgery. In particular, the criteria used to define a vein as suitable for grafting rather than use a prosthetic alternative may vary between the studies. The policy in this unit is to favour strongly the use of vein in preference to prosthetic graft whenever possible. It seems unlikely, therefore, that more 'diseased' veins with greater pre-existing abnormalities were used in the other studies[7,8] with consequently different results.

The anatomical intima and media of the vein wall has been measured before grafting; no difference was detected in either of these features between grafts that stenosed and those that did not. Although Marin and co-workers[7] promoted vein biopsy at the time of grafting as a means of identifying 'at risk' grafts, after the experience of 50 infrainguinal vein grafts the authors have now abandoned this practice. The morphology of the long saphenous vein does not appear to play a major role in the aetiology of vein bypass graft stenosis.

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British Journal of Surgery 1996, 83, 1380–1382

Colour duplex ultrasonography in the rational management of chronic venous leg ulcers

A. J. GRABS, M. C. WAKELY, I. NYAMEKYE, A. S. K. GHAURI and K. R. POSKITT

Cheltenham General Hospital, Sandford Road, Cheltenham GL53 7AN, UK
Correspondence to: Mr K. R. Poskitt

Colour duplex ultrasonographic imaging has largely replaced venography in the assessment of lower-limb venous disorders. This is a study of the use of duplex in the management of patients with chronic venous ulceration in community ulcer clinics. Patients with chronic leg ulceration and an ankle : brachial pressure index of 0·85 or greater were studied. Assessment of venous competence in both the deep and superficial systems of the affected and unaffected legs was performed using colour venous duplex imaging. Reflux was defined as reverse flow for greater than 1 s after manual calf compression. One hundred consecutive patients were assessed over 15 months. Of 111 ulcerated legs, 96 had active ulceration, while 15 had been ulcerated within the previous 6 months. Fifty-seven (51 per cent) of the 111 ulcerated legs had superficial incompetence alone (88 per cent long saphenous system or its perforators, 12 per cent short saphenous system). Six legs (5 per cent) had isolated deep venous incompetence. Forty-two legs had mixed superficial and deep venous reflux; 22 of these had undergone previous venous surgery. Colour venous duplex assessment demonstrated superficial venous disease in approximately half of limbs with chronic leg ulceration. Venous dysfunction in these patients is potentially curable by surgery.

Chronic leg ulceration is a relapsing condition with a prevalence of between 1·1 and 1·8 per cent; approximately 1 per cent of the population will develop leg ulceration during their lifetime[1–3]. In the UK there is an ulcer-prone population of about 400 000 patients of whom one-quarter will have active disease at any one time. Throughout the UK venous ulcer treatment accounts for 1·3 per cent of the total health care budget and up to 90 per cent are treated in the community[4]. Over 75 per cent of all leg ulcers have underlying venous pathology which can be treated with elevation and compression bandaging. However, successful treatment is followed by high recurrence rates ranging from 22 to 69 per cent at 1 year[5–7].

Use of central diagnostic and advisory services under the direction of vascular surgeons allows the underlying aetiology to be established. This may improve the overall success of treatment and reduce the burden on health resources[8–10]. Colour duplex ultrasonography is a fast and non-invasive assessment, gives anatomical and functional information, and has largely replaced venography in the assessment of lower-limb venous disorders[11–13]. Primary use of duplex to identify patients with chronic venous ulceration in whom surgery might be of benefit is reported.

Patients and methods

Patients referred to community-based leg ulcer clinics were studied. Patients were included in the study if ulceration was active or had been present within the previous 6 months. A chronic ulcer was defined as being present for at least 1 month. Patients with an ankle : brachial pressure index below 0·85 were excluded from the study. A standard pro forma was used to record clinical details of the ulcer such as a history of previous and present ulcers, previous deep venous thrombosis, varicose vein surgery or hip surgery. Both limbs were examined for venous disease, and the site and size of ulceration recorded. The ulcer site was defined as follows. zone 1, the foot; zone 2, the gaiter area extending from 2·5 cm below the malleoli to the point where the calf muscles become prominent posteriorly; and zone 3, extending above this point to the knee[8]. Ulcers that extended across zones were classified according to the zone with the major component of ulceration.

Colour venous duplex imaging of both legs was performed with a H.P. 1000 (Hewlett Packard, Massachusetts, USA) using a 7·5- or 4·5-MHz probe depending on leg size. Venous imaging assessed patency and competence of both the superficial and deep venous systems and the above- and below-knee perforating veins. Imaging of the common and superficial femoral veins, the saphenofemoral junction and the long saphenous venous system was done with the patient sitting on the edge of a variable height couch with the examined limb resting on a step and the hip slightly flexed and abducted. The presence of venous reflux was defined as reverse flow for greater than 1 s after manual calf compression. Thigh and below-knee perforating veins were assessed by examination of the long saphenous vein at the above-knee level following application of a tourniquet to the upper thigh and at the midcalf level with the tourniquet just below the knee. The saphenopopliteal junction and short saphenous vein were examined with the leg resting on a step, slightly flexed at the knee.

Vein competence at all sites was classified according to the following criteria: type I, superficial venous incompetence (including perforators); type II, deep venous incompetence; and type III, superficial and deep venous incompetence

Results

One hundred consecutive patients with venous ulcers were assessed over 15 months. There were 66 women and 34 men with a mean age of 69 (range 29–95) years. Active ulceration had been present for a mean period of 11 (range 1–240) months. Seven patients had diabetes mellitus and five rheumatoid arthritis. The majority of patients had unlimited mobility (*Table 1*). Eleven patients had bilateral ulcers, giving a total of 111 legs with 'ulcer disease' within the preceding 6 months and 89 contralateral limbs without previous ulceration within the preceding 6 months. The incidence of deep venous thrombosis, hip or knee surgery and varicose vein surgery for ulcerated and non-ulcerated legs is shown in *Table 2*. Ninety-six legs (86 per cent) were ulcerated at the time of

Paper accepted 24 April 1996

duplex assessment while 15 had been ulcerated within the previous 6 months. Forty-three (39 per cent) of the 111 legs had first-time ulcers and 68 (61 per cent) had recurrent ulcer disease. Sixteen legs (14 per cent) had multiple ulcers. Of the non-ulcerated legs, 19 (18 per cent) had suffered one previous episode of ulceration and 15 (14 per cent) had had ulceration on more than one occasion. A total of 106 (95 per cent) of the ulcers occurred in zone 2, and there were two ulcers in zone 1 and three in zone 3.

Duplex findings were as follows (*Table 3*). In legs with ulcers, 57 had type I superficial incompetence in the absence of deep venous incompetence. The long saphenous system or its perforators showed reflux in 88 per cent of limbs, with the short saphenous system accounting for 12 per cent. Eighteen (32 per cent) of these legs with superficial incompetence alone had previously undergone venous surgery; 12 ulcers had recurred in the operated system. Six legs (5 per cent) had deep venous reflux alone (type II). Forty-two limbs (38 per cent) had mixed superficial and deep incompetence (type III). Incompetence of the deep venous system was of the superficial/common femoral vein in two (of 42 legs), femoral and popliteal veins in 20, and the popliteal vein alone in 20. Twenty-two type III legs had undergone previous venous surgery.

Table 1 Aetiological factors and mobility of 100 patients with venous ulcers

	No of patients
Diabetes mellitus	7
Rheumatoid arthritis	5
Mobility status*	
I–chairbound	0
II–housebound	1
III–limited mobility beyond house	5
IV–mobile with walking aid	29
V–unrestricted	65

*Classified according to Baker *et al.*[5]

Table 2 Frequency of deep venous thrombosis, major orthopaedic procedures and venous surgical procedures (excluding sclerotherapy)

	Ulcerated limbs (*n* = 111)	Non-ulcerated limbs (*n* = 89)
Deep vein thrombosis		
Suspected	10 (9)	4 (4)
Proven	5 (5)	1 (1)
Hip or knee joint surgery	11 (10)	9 (10)
Previous venous surgery	43 (39)	29 (33)

Values in parentheses are percentages

Table 3 Venous reflux abnormalities on colour duplex ultrasonography

	Ulcerated limbs (*n* = 111)	Non-ulcerated limbs (*n* = 89)
Type I (superficial system alone)	57 (51)	46 (52)
Type II (deep system alone)	6 (5)	6 (7)
Type III (deep and superficial)	42 (38)	20 (22)
Occluded deep system	2 (2)	0 (0)
Normal study	4 (4)	17 (19)

Values in parentheses are percentages

Eleven patients had previous hip or knee surgery. Deep venous abnormalities were found in six legs, five having reflux disease and one occlusive disease. In the six patients who had significant restriction of mobility (grade I–III), only one had a normal venous duplex scan, three had superficial venous dysfunction and two deep venous dysfunction. Of the 15 ulcerated limbs with a suspected or proven deep vein thrombosis, 14 were demonstrated to have deep venous incompetence or occlusion; the popliteal system was abnormal in all 14 limbs.

Discussion

Knowledge of the underlying superficial or deep venous pathology allows logical management of patients with chronic venous ulceration. Although both types respond to elevation and compression, superficial venous disease may be corrected by surgery. Elevation and compression therapy in community leg ulcer clinics run by specialist nurses heals 80 per cent of venous leg ulcers, with 50–75 per cent healing within 12 weeks of commencing therapy[10,14,15]. Recurrent ulceration is common after such conservative management and can be predicted from knowledge of the underlying venous abnormality[11,14,16–18]. Moffatt *et al.*[19] reported a recurrence rate of 26 per cent at 1 year, with others demonstrating recurrence rates of up to 69 per cent at 2 years[7,20]. As poor compliance regarding compression hosiery and elevation is the usual cause of ulcer recurrence, other more permanent methods of treating venous hypertension may influence long-term results.

In this study duplex was the primary investigation of all patients with lower-limb ulceration. Duplex showed superficial venous reflux alone in over 50 per cent of limbs. These patients could be offered superficial venous surgery with the expectation of preventing recurrent ulceration. In this series, 34 per cent of patients with type I superficial disease had undergone previous venous surgery and, of these, two-thirds had recurrence in the operated venous system. Some 38 per cent of ulcerated legs had duplex evidence of both superficial and deep venous incompetence and, of these, half had undergone previous venous surgery which may have been inappropriate.

In this series, 95 per cent of patients with mixed superficial and deep venous incompetence had popliteal vein incompetence. This is in agreement with previous reports suggesting that the popliteal vein is the gatekeeper of the lower limb[11,21]. Fourteen of the 15 ulcerated limbs with proven or suspected deep vein thrombosis showed popliteal vein dysfunction. There is debate, fuelled by the recent development of subfascial endoscopic ligation of perforating veins, whether surgery has a role in these patients[22]. Correction of all sites of deep to superficial incompetence, including perforators, may improve deep venous function although outcome appears to be related to preoperative popliteal vein function[11,23].

Venous disease is often present in the contralateral non-ulcerated leg; indeed, 33 per cent of the contralateral legs had a history of previous ulceration. These results confirm the phlebographic findings of Stacey and colleagues[24], who stressed the importance of assessing the non-ulcerated limb in patients with leg ulcers.

Colour duplex imaging allows fast and non-invasive assessment of venous pathology in patients with leg ulcers. There was a high incidence of superficial venous disease alone in patients referred to these community-based leg ulcer clinics in whom surgery might be expected to be beneficial. Increasing numbers of patients are treated in specialist leg ulcer clinics and improved healing rates can be achieved. Currently, no emphasis has been placed on identifying patients who may benefit from surgical correction of venous incompetence. Colour duplex ultrasonography is the optimal investigation to define the exact pathology in the venous system so that appropriate treatment options can be discussed with the patient.

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British Journal of Surgery 1996, 83, 1383–1384

Surgical workshop

New graft design to inhibit myointimal hyperplasia in small vessel anastomoses

J. A. BRENNAN, M. A. ENZLER,
A. DA SILVA, T. V. HOW* and P. L. HARRIS
*Department of Vascular Surgery, Royal Liverpool University Hospital and *Department of Clinical Engineering, University of Liverpool, Liverpool, UK*
Correspondence to: Mr J. A. Brennan, Department of Vascular Surgery, 8C Link, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

Femorodistal bypass in patients in whom autologous vein is either absent or unsuitable requires the use of prosthetic materials, of which expanded polytetrafluoroethylene (PTFE) is the most widely used. Acceptable limb salvage can be achieved but the results are poorer than with vein. The majority of graft failures occur in relation to the distal anastomosis; they are due to a combination of technical problems encountered when suturing a rigid large bore graft to a small artery and to the rapid development of myointimal hyperplasia in the early postoperative period which results in narrowing of the outflow tract. To overcome these problems the use of an interposition cuff or patch of vein at the distal anastomosis has been advocated[1,2]. The most widely adopted of these is probably the Miller cuff and there is now evidence from a randomized study of significantly improved graft patency compared with no cuff when the distal anastomosis is below the knee joint[3].

In addition to facilitating construction of the distal anastomosis, the presence of a cuff seems to suppress the development of myointimal hyperplasia. The reason for this is not known but there is now some evidence to suggest that the geometric configuration of the cuff alters blood flow at the distal anastomosis in a predictable and beneficial way. In both bench and *in vivo* studies stable coherent vortices are seen to form during the deceleration phase of the cardiac cycle, persisting into diastole[4]. It is postulated that this non-turbulent flow pattern has the dual effect of maintaining high shear stresses and preventing preferential accumulation of blood products at critical sites within the anastomosis, both of which would reduce the propensity for myointimal hyperplasia. If the geometric configuration is the significant factor it may be that the presence of the vein is not important and that creation of a suitably shaped end to the graft may be all that is required.

Materials and methods

Externally supported 6-mm standard wall PTFE (Impra, Tempe, Arizona, USA) was used. The external spiral stent was removed from the distal 4 cm of the graft and a colonic balloon catheter of diameter 18 mm and length 30 mm (Boston Scientific, St Albans, UK) was inserted. The balloon was then fully inflated with water up to its full size (not exceeding 6 atmospheres) using a pressure-gauge syringe with a screw hub. Preliminary studies confirmed that the PTFE grafts used could safely withstand a threefold increase in diameter without rupture and with minimal (less than 5 per cent) recoil. The Miller cuff configuration was then created by cutting across the inflated segment at an angle of 45°, starting at the point of maximum diameter (*Fig. 1*). The final shape was created by minimal trimming. The graft was then resterilized with ethylene oxide gas.

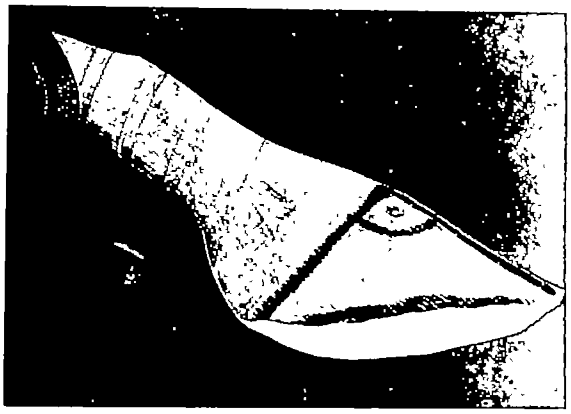

Fig. 1 End of the graft after balloon dilatation and shaping

Clinical studies

Grafts prepared in this fashion have now been used in a small number of patients in whom there was no available autologous vein and the distal anastomosis was below the knee joint. The dilated graft segment has proved easier to handle than the normal graft, with less tendency to turn in, thus facilitating construction of the distal anastomosis. Formal assessment of these grafts is at an early stage but all remain patent and preliminary studies have suggested that similar flow patterns to those seen in both the bench model and the *in vivo* studies of the standard Miller cuff are observed in the precuffed grafts.

Discussion

There is increasing evidence to support the use of an interposition vein cuff at the distal anastomosis between a synthetic graft and a small artery. Much of the impetus for use of a piece of vein stemmed from the belief that it buffered the compliance mismatch between a rigid graft and a smaller, softer artery. There is, however, no scientific evidence to support this hypothesis and other theories must be considered. Preliminary work looking at flow changes at cuffed anastomoses raises the possibility that it may be the anatomical configuration of the cuff rather than the nature of its constituent parts which confers the benefit. Further studies are required before these matters can be resolved and close follow-up of implanted grafts is vital. The early results, however, have encouraged the authors to continue with this line of research.

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British Journal of Surgery 1996, 83, 1384–1385

Short note

Exclusion from day surgery: a 1-year clinical audit

S. K. CLARK, J. P. GRIEVE and
P. E. M. JARRETT
Department of Surgery, Kingston Hospital National Health Service Trust, Kingston upon Thames, UK
Correspondence to Miss S. K Clark, Imperial Cancer Research Fund Colorectal Cancer Unit, St Mark's Hospital, Northwick Park, Harrow HA1 3UJ, UK

Introduction of day surgery increases the efficiency of provision of surgical services. It is endorsed by the Royal College of Surgeons of England[1], and the Audit Commission[2] which has also identified obstacles to its fuller use, including lack of information to assess performance, estimate potential and monitor change[2]. National[2,3] and local audits address issues such as outcome, admission rates and use of facilities. The problem of patients admitted for inpatient surgery who would be suitable for day surgery has not been raised, and these patients are not detected by day unit-based audit. A 1-year prospective study was undertaken of patients added to waiting lists for inguinal hernia repair or ligation and stripping of varicose veins to examine the reasons for rejecting day surgery.

Patients and methods

A record was made of every patient with inguinal hernia or varicose veins when operation was planned. When anyone was added to the inpatient waiting list, reasons why they were considered unsuitable for day surgery were noted by the booking clinician. At the end of the study these indications for admission were reviewed, alongside patients' notes, by the consultant surgeons responsible for the day unit, who assessed whether they were bona fide or whether the patient would actually have been suitable for day surgery.

Results

Some 277 patients were booked for inguinal hernia repair, 160 (58 per cent) as day cases, and 346 patients for varicose vein surgery, 271 (78 per cent) as day cases. The reasons for exclusion from day surgery and their validity are detailed in *Table 1*. Had all been booked appropriately, 63 per cent of inguinal hernia repairs and 88 per cent of varicose vein surgery would have been planned as day cases.

Table 1 Reasons for exclusion from day surgery

	Inguinal hernia repair	Varicose vein surgery
Medical conditions		
ASA grade II		
Asthma	1*	1*
Hypertension	1*	4*
ASA grade III	22	15
Body mass index more than 30	3	3
Psychiatric disorder	2	2
Disability impairing mobility	5	0
Detached retina	1*	0
On warfarin	1	1
Jehovah's witness	0	1*
Previous deep vein thrombosis	0	1
Pregnant	1	0
Age more than 90 years	2*	0
Surgical		
Recurrent hernia or varicose veins	20	11
Bilateral hernia or varicose veins	19	22*
Large hernia	9	0
Leg ulcer	0	1
Other procedure required		
Transurethral prostatectomy	1	0
Epididymal cyst	1	0
Varicose veins	1	0
Haemorrhoidectomy	2	0
Anal stretch	1*	0
Hydrocele	1	0
Ingrowing toenail	1*	0
Social		
Distance from home	1*	1*
Alone at home	6*	1*
Patient request	1	0
No reason given or incomplete information	14	9
Clerical error at booking	0	2*
Total booked as inpatients	117	75
Avoidable admissions	14	32

*Reason considered invalid on review. ASA, American Society of Anesthesiologists

Discussion

Selection criteria similar to those used elsewhere[1,4,5] have been agreed between surgeons and anaesthetists locally and are available in the outpatient department. Restrictions on day surgery because of social circumstances have been largely overcome by having a hospital hotel where patients may stay.

Paper accepted 19 April 1996

Most of the patients booked incorrectly as inpatients had been seen by junior staff new to the hospital. It is likely that they were unclear of differences in selection criteria between hospitals and were unaware of the hotel facilities. Clerical error was the only other repeated cause of misbooking.

The authors intend to avoid unnecessary inpatient admissions by documenting procedures considered suitable for day surgery locally and bringing these, the anaesthetic guidelines and details of the hotel to the attention of new staff before arrival and incorporating them into a redesigned booking form. Matters might be improved further by monitoring the inpatient waiting list, so that every case booked for an operation usually performed in the day unit is brought to the attention of the appropriate consultant.

In a unit performing well beyond the targets suggested by the Audit Commission[2], clinical audit has revealed room for improvement that can be implemented by the adoption of a few simple measures. Continued audit of inpatient admissions alongside day unit activity will identify whether these measures have been effective.

Acknowledgements

The authors thank Mr R. D. Leach and Mr C. J Cahill for help in completing this study

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British Journal of Surgery 1996, 83, 1386–1389

A 4-year prospective audit of the cause of death after infrarenal aortic aneurysm surgery

A. J. P. SANDISON, Y. PANAYIOTOPOULOS, R. C. EDMONDSON, M. R. TYRRELL and P. R. TAYLOR

Departments of Surgery, Guy's and Lewisham Hospitals, London, UK
Correspondence to: Mr P R. Taylor, Department of Surgery, 2nd Floor New Guy's House, Guy's Hospital, St Thomas Street, London SE1 9RT, UK

This study was a 4-year prospective audit of abdominal aortic aneurysm surgery including 222 aneurysm repairs: 106 elective, 76 urgent and 40 emergency. Twenty-five patients died: four who underwent elective surgery, seven urgent and 14 emergency. The two major causes of death, multiple organ failure and colonic ischaemia, were responsible for 11 of the 25 deaths. The three deaths from myocardial infarction all occurred in patients with a leaking aneurysm. Blood loss was significantly higher in patients with multiple organ failure and in those with colonic ischaemia. Methods to identify patients at high risk of massive blood loss and colonic ischaemia may be a way to reduce mortality.

Over the past 30 years the mortality rate from elective repair of abdominal aortic aneurysms (AAAs) has declined from over 15 per cent[1] to less than 5 per cent[2]. Some authors have suggested that elective mortality rates greater than 5 per cent are 'unacceptable and any surgical unit which consistently fails to achieve this figure should not continue to perform this kind of surgery'[3]. In contrast, reported mortality rates for repair of ruptured AAAs have not declined significantly and a recent audit[4] suggests that there is a wide variation in the mortality rate, from 47 to 70 per cent. The mortality rate from rupture, including deaths in the community, was found to be as high as 94 per cent[5].

This study describes the results of a prospective computerized audit of 222 AAA repairs undertaken over a 4-year period. The main causes of death were analysed to look for ways in which the outcome may be improved.

Patients and methods

All patients who had AAA repair between September 1991 and July 1995 under a single vascular consultant (P.R.T.) were entered into a prospective computerized audit. The details recorded are shown in *Table 1*. These were entered on to a custom-designed vascular database developed from Superbase IV (Software Publishing, Bracknell, UK), a Windows-based PC database program. Demographic details were entered on the patient's admission to hospital, and details of the medical history were taken from the patient's notes at the time of surgery. Operation details were recorded immediately after surgery and subsequent progress was entered at the time of discharge from hospital and at a routine 6-week outpatient review. During this interval the consultant provided an *ad hoc* one in one vascular emergency cover to two hospitals as well as performing all elective vascular surgery at both hospitals. Thus almost all the patients admitted to either of the two hospitals for aneurysm surgery are included.

All patients who presented electively with asymptomatic AAAs with a diameter of 5·5 cm or greater were considered for repair unless they had widespread malignancy or were receiving oxygen therapy at home. Aneurysms measuring between 4·0 and 5·5 cm were entered into the small aneurysm study. No upper age limit was applied for elective surgery; instead an attempt was made to assess physiological rather than chronological age. Patients with symptomatic aneurysms (tenderness, back pain or embolic complications) were offered urgent surgery. Those who reached hospital with a ruptured aneurysm had emergency surgery unless they were over 80 years of age with a blood pressure of less than 80 mmHg, despite initial fluid resuscitation.

Table 1 Details recorded in the computer database

Patient demographic details
Risk factors for atherosclerosis: smoking, hypertension, diabetes, hyperlipidaemia, gout, renal failure
No of drugs taken
Symptoms and signs of arterial occlusive disease
Cardiac symptoms
Cerebrovascular symptoms
Intervention details: urgency
Operation
Name of surgeon
Grade of surgeon
Heparin dose
Operating time
Blood loss
Graft details
Inflow vessel
Outflow vessel
Complications
Comments
Outcome

Some 190 patients were men and 32 women. The median age was 71 (range 49–89) years. None of the elective, 11 of the urgent and six of the emergency cases were tertiary referrals. In the study interval three patients were refused elective surgery on the basis of advanced cardiac, respiratory or renal disease not amenable to improvement by intervention.

The principal operator was the consultant in 35 per cent of cases, the senior registrar in 54 per cent and the registrar in 11 per cent, the latter two under supervision.

Results

A total of 222 aneurysm repairs were performed; 106 (48 per cent) were elective, 76 (34 per cent) were urgent and 40 (18 per cent) were emergency repairs for ruptured aneurysms. The commonest risk factor was smoking (68 per cent), followed by hypertension (35 per cent), renal failure (7 per cent) and diabetes (6 per cent). All patients received prophylactic antibiotics. A tube graft was used in

Paper accepted 7 July 1996

67 per cent of repairs, a bifurcated graft to the iliacs in 29 per cent and a bifurcated graft to the femoral arteries in 4 per cent. The external iliac artery was used in preference to the femoral arteries as an outflow site wherever possible to minimize the incidence of graft infection. The inferior mesenteric artery was not reimplanted. The median length of stay in hospital was 12 (range 7–32) days for elective cases, 12 (range 4–80) days for urgent cases and 12 (range 0–182) days for emergency cases.

Table 2 Causes of death in four patients undergoing elective repair of abdominal aortic aneurysm

Cause of death	No. of patients	Comment
Multiple organ failure, ischaemic right colon	1	Heavy bleeding from lumbar vessels during operation causing large blood loss. Laparotomy on day 7 for sepsis; necrotic right colon resected. Died 2 days later
Pneumonia	1	*Staphylococcus aureus* and *Escherichia coli* cultured from sputum
Cerebrovascular accident	1	Nephrectomy 6 weeks before AAA repair for hypernephroma. Adrenalectomy performed at AAA repair for metastasis. On day 6 following AAA repair had massive stroke which computed tomography showed to be a bleed into cerebral metastasis
Aspiration	1	Uneventful AAA repair. Readmitted on day 27 with small bowel obstruction. Aspirated under anaesthesia during laparotomy. Died the next day

AAA, abdominal aortic aneurysm

Table 3 Causes of death in seven patients undergoing urgent aneurysm repair

Cause of death	No. of patients	Comment
Multiple organ failure	3	Very friable aorta. Resuture of proximal anastomosis. Developed renal, cardiac and respiratory failure. Treatment withdrawn on day 19
		Returned to theatre for bleeding from top anastomosis. Massive blood loss. Became inotrope dependent. Died on day 19
		Died on day 19 after initially developing renal failure
Ischaemic colitis	1	Died after prolonged ventilation
Pulmonary embolus	1	Received prophylactic subcutaneous heparin throughout stay
Paraplegia	1	Also developed renal failure Treatment withdrawn after discussion with family
Respiratory failure	1	Impossible to wean from the ventilator. Subsequent investigation showed carcinoma of the bronchus

Overall 25 patients (11 per cent) died within 30 days of surgery. Four had undergone elective repair, seven urgent repair and 14 emergency repair. The causes of death in the elective, urgent and emergency cases are shown in *Tables 2, 3* and *4* respectively. *Table 5* lists the complications according to category of surgery.

Recorded blood loss was compared between patients with the Mann–Whitney *U* test. There was no significant difference in blood loss between elective and urgent cases, but a highly significant difference between elective and emergency cases ($P < 0{\cdot}0001$) and between urgent and emergency cases ($P = 0{\cdot}0001$) (*Fig. 1*). There was no significant difference in median blood loss between patients who had a postoperative myocardial infarction (1200 (range 100–7000) ml) and those who did not (1200 (range 100–15 000) ml). Patients who had a bifurcated graft lost more blood than those with a tube graft (1700 *versus* 1200 ml, $P = 0{\cdot}04$). Patients who developed colonic

Table 4 Causes of death in 14 patients undergoing emergency aneurysm repair

Cause of death	No. of patients	Comment
Multiple organ failure	4	Hypotensive for 10 min before clamping. Died on day 5
		On warfarin Died on day 4
		Torrential bleeding. Abdomen packed to control. Colon ischaemic on day 3. Died on the same day
		Good initial result then developed renal failure. Re-explored as became septic but nothing found. Died on day 19
Myocardial infarction	3	Myocardial infarct on day 4
		Myocardial infarct on day 8
		Myocardial infarct on closing abdomen Unresponsive to inotropes
Bleeding	3	Died on table. Retroaortic renal vein
		Aorta would not hold sutures. Massive blood loss
		No blood clotting products available
Ischaemic colitis	2	Both left-sided colon
Reperfusion	1	White legs in intensive care unit. Returned to theatre and aortobifemoral graft performed. Developed reperfusion syndrome with renal failure. Autopsy showed large bronchial carcinoma
Cerebrovascular accident	1	Died 8 days after operation

ischaemia lost significantly more blood than those who did not (8000 *versus* 1200 ml, $P = 0{\cdot}002$). Those who developed multiple organ failure lost significantly more blood than those who did not (5000 *versus* 1200 ml, $P < 0{\cdot}001$). Patients who died lost significantly more blood than those who survived (5000 *versus* 1100 ml, $P < 0{\cdot}0001$).

There was no significant difference in duration of operation between elective, urgent and emergency cases, between survivors and non-survivors, and between those who developed multiple organ failure or colonic ischaemia and those who did not.

There were three late complications. One aortoenteric fistula presented 6 months after the initial surgery and was treated by removal of the graft and insertion of bilateral axillofemoral grafts. However, this patient became septic while in hospital and refused further treatment; post-mortem examination showed acute diverticular disease. Two patients developed incisional hernias that did not require surgical repair.

Table 5 Complications in patients undergoing elective, urgent and emergency aneurysm repair

Complication	Elective	Urgent	Emergency
Pneumonia	6	7	6
Re-exploration for bleeding	3	3	0
Myocardial infarction	1	2	2
Distal embolus	1	1	0
Gastrointestinal bleed	1	0	0
Pneumothorax (from central venous line)	1	0	0
Renal failure			
Haemofiltration	0	1	5
Haemodialysis	0	0	1
Spinal cord ischaemia	0	1	0
Deep vein thrombosis	0	0	2
Pulmonary embolus	0	1	0
Bleed from chest (combined CABG and AAA repair)	0	1	0
Small bowel obstruction	0	0	1
Diathermy burn	0	0	1

CABG, coronary artery bypass grafting; AAA, abdominal aortic aneurysm

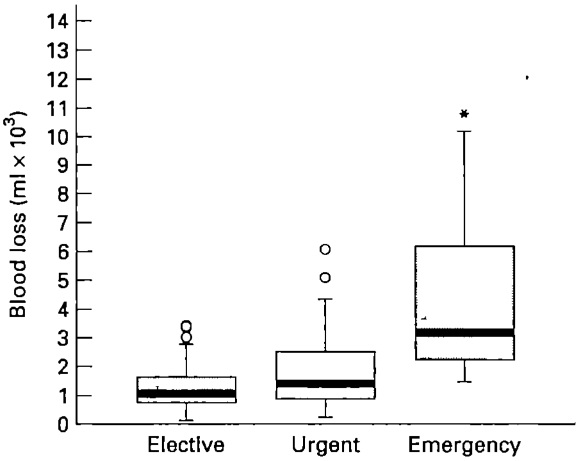

Fig. 1 Boxplot comparing blood loss in elective, urgent and emergency aortic aneurysm repair. Values are: median (dark line), interquartile range (box), full range (whiskers), outliers (O) and extremes (*). $^*P = 0{\cdot}0001$ (emergency *versus* elective and urgent operations, Mann–Whitney *U* test)

Discussion

The mortality rates for elective, urgent and emergency surgery in this series were similar to those in other recent reports[6,7]. Although cardiac complications are considered to be the major cause of morbidity and mortality after aortic aneurysm repair, this was not confirmed in the present series. Myocardial infarction accounted for only three of the 25 deaths and these occurred only in patients undergoing emergency operation. Myocardial infarction comprised 10 per cent of the morbidity in all groups. The diagnosis of myocardial infarction in this series was based on a combination of clinical symptoms or electrocardiographic change associated with a significant rise in the creatinine kinase MB isoenzyme. Because of the high incidence of severe coronary artery disease in patients with aneurysms[8], many recommendations have been made regarding the preoperative cardiac investigations that should be performed in patients undergoing elective aneurysm repair. A recent report[9] showed that there is still a wide variation between hospitals in preoperative cardiac investigation. Patients having elective aneurysm repair routinely had resting electrocardiography and transthoracic echocardiography in this hospital; however, echocardiography detected only four at-risk patients, all of whom could have been recognized by the history and physical examination. Three patients were assessed by coronary angiography, and two were found to have untreatable ischaemic heart disease and were treated conservatively. One patient underwent coronary artery bypass grafting before aortic surgery, and a fourth had unrecognized hypertension that was treated for 3 months, after which he had uneventful aortic surgery. In view of the low rate at which echocardiography actually alters management, the authors have now changed their policy and rely on a detailed history and clinical examination combined with resting electrocardiography only. Patients identified as high risk are referred to a cardiologist for further assessment.

The two major causes of death in this series were multiple organ failure and ischaemic colitis (11 of 25 deaths). This confirms a recently reported series[6] which also found multiple organ failure to be the most important cause of death. The incidence of multiple organ failure was higher in urgent and emergency cases than in elective cases. Multiple organ failure in patients with ruptured AAAs was first described by Tilney *et al.*[10] in 1973 in a series of 18 patients. In the report by Huber *et al.*[6] it was noted that the operating time was significantly longer in non-survivors (7·7 *versus* 5·7 h in survivors) but that there was no significant difference in estimated blood loss between these two groups. However, there was no separate analysis to compare those with and without multiple organ failure. In discussing the results of Huber and co-workers[6], Hollier commented that in his experience 'multiple organ failure after aortic surgery is generally limited to those patients requiring large amounts of blood and crystalloid fluids or those who undergo suprarenal clamping'. The present results confirm the significant association between blood loss and the development of multiple organ failure. It is unclear exactly how these are related. It could be the blood loss itself, the hypotension consequent to the blood loss, or the massive transfusion of homologous blood. Colonic ischaemia, if progressive, may cause multiple organ failure by producing septic shock. It is interesting to note that in this series the development of colonic ischaemia was associated with large blood loss. An explanation for this may be the postoperative use of high concentrations of inotropic drugs, which cause splanchnic vasoconstriction and exacerbate any tendency to colonic ischaemia.

Intestinal ischaemia followed by reperfusion causes acute lung injury in animal models[11], but the mechanism for this is unclear. There is no direct evidence of bacterial translocation[12] but high endotoxin levels have been demonstrated in systemic blood during aortic cross-clamping[13], suggesting that this could, in association with hypotension resulting from massive blood loss, be a trigger for a systemic inflammatory response that may lead to multiple organ failure.

Clearly, massive blood loss is unavoidable in most cases, particularly where an aneurysm has ruptured. The use of autotransfusion may be a more realistic way of reducing the need for transfusion of large quantities of homologous blood in these patients.

Respiratory complications were the commonest cause of morbidity in all categories of patient. Calligaro *et al.*[14] showed in a retrospective review that seven factors were independently associated with the development of major pulmonary complications after aortic surgery. Of these, only poor lung function on respiratory testing may be amenable to improvement before operation. Of note is the fact that infusing large volumes (more than 6 litres) of crystalloid was associated with pulmonary complications.

This prospective audit has shown that the major causes of death after aneurysm repair are multiple organ failure and colonic ischaemia. The previously reported high incidence of cardiac complications has not been confirmed. Both multiple organ failure and colonic ischaemia have been shown to be associated with large perioperative blood loss. Avoidance of large blood loss, whilst clearly desirable, is not always possible. The use of autologous blood transfusion in these circumstances may be beneficial.

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British Journal of Surgery 1996, 83, 1390–1393

Management cost of acute limb ischaemia

B. D. BRAITHWAITE, L. JONES, B. P. HEATHER, P. A. BIRCH and J. J. EARNSHAW

Departments of Surgery and Radiology, Gloucestershire Royal Hospital, Gloucester, UK
Correspondence to Mr B. D. Braithwaite, Queen's Medical Centre, Nottingham NG7 2UH, UK

The cost of attempting limb salvage in patients who presented with acute lower limb ischaemia was recorded prospectively for 20 months. Seventy-five patients were admitted during the study; 45 were treated primarily by radiological intervention and 18 had primary surgery. The remainder were treated conservatively. Patients who had primary surgery required fewer visits to the operating theatre than those who had primary thrombolysis, but there was no difference in the total time that the theatre or radiology suite was occupied: median 2·3 (10th centile range 1·5–5·0) h and 3·0 (2·0–5·0) h respectively. Median (range) cost of disposables for performing surgery was £82 (58-169) and for thrombolysis was £407 (252–596). When the costs of using the theatre or radiology suite were included, the costs of both treatments were similar: surgery £683 (309–1438) and lysis £861 (611–1244). Median (10th centile range) inpatient stay for surgical patients was 9 (3-18) days and for those having thrombolysis 11 (2–29) days. Median (10th centile range) costs for bed occupancy were similar in both groups: surgery £2497 (643–9115) and lysis £2189 (902–6020). Mean cost for attempting limb salvage by surgery was £3429 (1094-10 065) compared with £3230 (1543–8353) for thrombolysis.

The advantage of thrombolysis compared with conventional catheter embolectomy or primary bypass appears to be a reduction in postoperative cardiorespiratory complications associated with surgery[1]. The outcome of thrombolysis, in terms of limb salvage, is comparable to that of surgery, but there is little information on the cost of the two treatments. To address this, the costs of primary thrombolysis and primary surgery in the management of acute arterial occlusion in a district general hospital were recorded prospectively for 20 months, at the same time as a multicentre randomized trial of high-dose bolus administration and low-dose infusion of tissue plasminogen activator (tPA) was in progress[2].

Patients and methods

A protocol for the management of acute limb ischaemia has been used at this hospital for 3 years. Patients who presented with sudden onset of acute arterial occlusion, with an obvious source of embolus and no previous history of peripheral vascular disease, were managed primarily with Fogarty catheter embolectomy and, if necessary, peroperative thrombolysis[3] Patients who did not satisfy the criteria for an embolus were systemically heparinized and then had diagnostic angiography. If there was evidence of neurosensory deficit, angiography was performed urgently; if not, it was carried out the following morning If the angiogram revealed a lesion suitable for intra-arterial thrombolysis patients were randomized either to low-dose infusion or high-dose bolus tPA treatment. All acute vascular admissions were managed by one of two consultant vascular surgeons who had close liaison with consultant radiologists specializing in vascular radiological procedures.

Between September 1993 and April 1995 the cost of treatment for all patients with acute lower limb ischaemia was recorded prospectively. The cost of treatment for primary thrombolysis and primary surgery was calculated using April 1995 prices.

Primary thrombolysis

A record was made of the number of visits to the radiology department and the duration of occupation of the angiography suite. This duration was multiplied by the hourly cost of running the suite (£147) producing a cost per patient for 'radiology time'. This running cost was obtained from the Radiology Directorate Finance Manager and was calculated from the gross annual departmental running costs, including depreciation, divided by the number of patients investigated, to produce a cost per hour (£110). Added to this were the hourly costs of non-medical staff in the suite: senior radiographer (£15), staff nurse (£12) and clerical costs (£10) These costs included routine and 'out-of-hours' workload as the Finance Manager was not able accurately to differentiate between the two. All disposable instruments used during the procedures, including those for secondary angioplasty, were noted, multiplied by the unit cost to the hospital, including value added tax, and added together to give a 'radiology disposables' cost (*Table 1*). Both disposables and radiology time were added to give a 'total radiology cost' If a patient required a secondary surgical procedure then the costs were calculated as for primary surgery (below).

Each patient who received thrombolysis was nursed, whenever possible, in a surgical high-dependency unit (HDU) bed during the tPA infusion and for the first day after catheter removal. If a bed was not available, patients were nursed on a standard 'open' surgical ward by nurses familiar with thrombolytic therapy. The cost for an HDU bed in this hospital was £450 per day or part

Table 1 Inventory and 1995 prices of disposable items used for thrombolysis

Item	Unit cost (£)	Item	Unit cost (£)
Angiogram pack	7·39	Rosen 1·5-mm J guide	18·50
4-Fr straight catheter	8·31	3-mm J guide	5·24
4-Fr pigtail catheter	17·80	15-mm J wire	8·20
5-Fr pigtail catheter	17·80	Angle Terumo guide	21·32
5-Fr straight catheter	13·50	Sidewinder guide	14·45
5-Fr Cobra catheter	14·45	Amplatz superstiff guide	19·60
6-Fr straight catheter	15·00	Terumo superstiff guide	19·20
Headhunter catheter	14·45	260-cm guide	11·90
5-Fr predilator	0·57	260-cm Terumo guide	19·85
4-Fr sheath	12·24	Straight Terumo guide	21·32
5-Fr sheath	12·24	Straight 120-cm guide	9·45
6-Fr sheath	14·00	Olbert PTA balloon	129·52
7-Fr sheath	0·57	tPA 50 mg	352·90
		tPA 20 mg	176·45

Prices exclude value added tax. PTA, percutaneous transluminal angioplasty; tPA, tissue plasminogen activator

Paper accepted 20 June 1996

Table 2 Inventory and 1995 prices of disposable items used for surgery and major haemorrhage

Item	Unit cost (£)	Item	Unit cost (£)
3-Fr embolectomy catheter	22·00	5/0 polypropylene suture	2·00
4-Fr embolectomy catheter	22·00	2/0 polyglycolic acid suture	1·90
5-Fr embolectomy catheter	22·00	3/0 polyglycolic acid suture	1·90
Arterial line	9·50	2/0 nylon suture	0·80
Single-lumen CVP line	25·50	2/0 chromic catgut suture	0·50
Vacuum drain	4·00	2/0 polydioxanone sulphate suture	1·90
Streptokinase 250 000 units	18·87	2/0 polyglactin suture	2·00
tPA 20 mg	176·45	Axillobifemoral graft	489·00
Packed red cells 450 ml	31·38	PTFE graft	770·00
Fresh frozen plasma 500 ml	17·43		

Prices exclude value added tax. CVP, central venous pressure; PTFE, polytetrafluoroethylene

thereof, for a ward bed £300 and, for the one patient who required it, an intensive therapy unit (ITU) bed was £700 per day. These costs included gross running costs of the Surgical Directorate, including non-medical staff. The duration of each patient's stay was multiplied by the cost for an ITU, HDU or ward bed to give a 'bed cost'. If patients required blood products, the cost of these was calculated and recorded as 'blood product cost', the price of blood products was obtained from the Department of Haematology. 'Total radiology cost', 'bed cost', and, where appropriate, 'total surgical cost' and 'blood product cost', were added to give a 'primary thrombolysis cost'. This was divided by the number of limbs salvaged 30 days after treatment to give a figure for the mean cost per limb salvaged.

Primary surgery

For patients who required surgery as a primary treatment, 'bed cost' and 'blood product cost' were calculated as for thrombolysis. 'Surgical time' was calculated by multiplying the time that a patient was present in the operating theatre suite, including time in recovery, by the hourly rate of £250 per hour. This hourly rate was supplied by the Operating Theatre Manager and, in a similar fashion to 'radiology time', was calculated from gross departmental costs, including non-medical staff and depreciation. Surgical disposables were, likewise, recorded for each patient (*Table 2*). If patients required thrombolysis after surgery, radiology costs were calculated as above. Primary surgery and mean surgical costs per limb saved at 30 days were calculated as for thrombolysis.

Data are expressed as median (10th centile range). Presentation of patient details and results are made in two parts: the cost of high-dose bolus therapy was compared with that of low-dose infusion, and analysis of patients' clinical details and financial variables was performed using Mann–Whitney analysis. For categorical data, χ^2 analysis was performed. The combined cost of both techniques of thrombolysis was compared with that of surgery but no statistical analysis was done.

Results

During the study period, 75 patients were admitted with acute lower-limb ischaemia. Forty-four were treated with primary thrombolysis, 18 had primary surgery, one had insertion of an iliac stent and 12 were treated conservatively because of their moribund clinical condition. Only data for those who received thrombolysis or surgery are presented and analysed.

Thrombolysis

There were no significant differences between the clinical features of patients who received high-dose bolus and low-dose infusion of tPA (*Tables 3* and *4*). There were statistically significant differences in treatment details: the high-dose group received higher total doses of tPA ($P=0{\cdot}003$) for a shorter duration ($P=0{\cdot}03$). After thrombolysis, more patients required adjunctive surgical intervention in the high-dose than the low-dose group (five *versus* zero, $P=0{\cdot}01$): In the high-dose group, of the three patients in whom lysis failed, one died from ischaemic bowel within 12 h of lysis, one had an urgent femorofemoral crossover graft and one had an emergency femoropopliteal bypass which thrombosed and was revised to a femorotibial bypass. This last patient also required fasciotomy. One patient with no run-off after lysis proceeded to a successful embolectomy while two other patients required an amputation. The remaining three patients were anticoagulated. The one patient with clinically useful lysis had a vein patch angioplasty and one patient with complete lysis rethrombosed and subsequently had a successful embolectomy. No adjunctive procedures were required in the low-dose group, but one patient with no run-off later had an amputation and a second patient received oral anticoagulant.

Table 3 Demographic details of patients who received thrombolysis with high-dose bolus or low-dose infusion of tissue plasminogen activator

	High-dose bolus tPA ($n=21$)	Low-dose infusion tPA ($n=23$)	P*
Median age (years)	72 (59–81)	74 (53–84)	0·42
Sex ratio (M:F)	13:8	14·9	0·94
Diabetes mellitus	5	6	0·86
Ischaemic heart disease	11	13	0·78
Peripheral vascular disease	12	17	0·24
Stroke	2	2	0·92
Aspirin therapy	9	9	0·80
Warfarin therapy	3	4	0·78
Median duration of ischaemia (h)	120 (13–470)	48 (7–403)	0·15
Audible ankle Doppler signal	6	5	0·60
Thrombus	18	16	0·20
Embolus	3	7	
Neurosensory deficit	13	8	0·07
Bypass graft involved	9	9	0·80

Values in parentheses are 10th centile range. tPA, tissue plasminogen activator. *Mann–Whitney U test

Table 4 Treatment and 30-day outcome of patients who received thrombolysis with high-dose bolus or low-dose infusion of tissue plasminogen activator

	High-dose bolus tPA ($n = 21$)	Low-dose infusion tPA ($n = 23$)	P*
Median total dose of tPA (mg)*	30 (20–41)	21 (12–33)	0·003
Median duration of infusion (h)*	5 (2–21)	20 (3–27)	0·03
Immediate outcome			
Complete lysis	11	18	0·07
Clinically useful lysis	1	3	0·39
Lysis but no run-off	6	2	0·09
Failed lysis	3	0	0·06
Secondary intervention			
Angioplasty	6	8	0·66
Adjunctive surgery	5	0	0·01
Outcome at 30 days			
Limb salvage†	16 (76)	19 (83)	0·60
Amputation†	3 (14)	0 (0)	0·06
Death†	2 (10)	4 (17)	0·38
Complications			
Major haemorrhage	2	3	0·71
Groin haematoma	1	0	0·30
Haematuria	1	0	0·30
Distal embolization	0	1	0·33
Catheter displacement	0	1	0·33
Reperfusion injury	1	0	0·30
Death during lysis	1	1	0·95

Values in parentheses are *10th centile range and †percentages. tPA, tissue plasminogen activator. *Mann–Whitney U test

Limb salvage rates and the incidence of major haemorrhage were similar in both groups. One patient in the low-dose group had a retroperitoneal bleed which required operative repair of the catheterized artery. He was transferred to the ITU where he died from a myocardial infarction. Two others needed blood transfusion because of catheter site haemorrhage. In the high-dose group, two patients needed operative repair of the direct graft puncture sites. Two patients died in the high-dose group: one from ischaemic bowel and another from acute limb ischaemia which was not reversed after lysis because of absent run-off. Four patients died in the low-dose group from myocardial infarction (two), pulmonary embolus (one) and general deterioration (one).

Surgery

Eighteen patients were treated with primary surgery. Eleven required femoral embolectomy alone, while four had embolectomy followed by a bypass graft. Two additional patients had emergency bypass procedures and one required a common femoral endarterectomy. Peroperative thrombolysis was carried out in three operations to clear distal run-off vessels seen to be occluded at the time of peroperative angiography. Only one patient had a fasciotomy. One patient required catheter-directed thrombolysis with tPA after rethrombosis following a superficial femoral artery embolectomy 5 days previously.

Complications occurred in eight patients: four of 18, patients had a major haemorrhage, one had a stroke and three went into renal failure after reperfusion of the ischaemic limb. This compares with five of 44 patients with major haemorrhage, no strokes and one reperfusion injury in the group who received thrombolysis. At 30 days, the limb salvage rate was seven of 18, amputation rate two of 18 and mortality rate nine of 18, compared with 35 of 44, three of 44 and six of 44 respectively in the group that received thrombolysis. Death in the surgical group was caused by cardiac arrest (two patients), renal failure (two), mesenteric ischaemia (two), pneumonia (two) and stroke (one).

Cost of thrombolysis

Median number of visits to the radiology suite for patients who received high-dose bolus therapy was 3 (range 2–4), the same as that for low-dose therapy, 3 (range 2–5) ($P = 0{\cdot}15$). Median time for occupying the radiology suite was 3·3 *versus* 3·0 h respectively ($P = 0{\cdot}43$). The cost of radiology disposables was significantly higher in the high-dose group, median (range) £427 (386–592) *versus* £353 (216–616) ($P = 0{\cdot}01$), and therefore the total radiology costs were higher for the high-dose group, £928 (717–1203) *versus* £790 (526–1286) ($P = 0{\cdot}05$). Patients who received high-dose therapy stayed in hospital significantly longer than those in the low-dose group (median 11 *versus* 8 days, $P = 0{\cdot}01$) and therefore incurred significantly higher bed costs (median (range) £2562 (886–8632) *versus* £2043 (862–3288) $P = 0{\cdot}02$) and primary thrombolysis costs, £4055 (1847–11 511) *versus* £2845 (1390–4398), $P = 0{\cdot}01$). Relatively few patients required surgery or blood products so these components were an insignificant part of the primary thrombolysis cost. In terms of cost per limb saved, low-dose thrombolysis was half as expensive as high-dose therapy (mean £6967 *versus* £3535).

Cost of primary surgery and primary thrombolysis

The median number of visits to the operating theatre was smaller in the surgical group than to the radiology department for patients having thrombolysis, 1 (range 1–3) *versus* 3 (1–4), but there was no difference in the total time that the theatre suite was occupied compared with total time in radiology (2·3 *versus* 3·0 h). Median hospital stay was similar in both groups (9 days for surgery *versus* 11 days for thrombolysis). The cost of disposables for performing thrombolysis was higher than that for surgery but the cost for theatre time was greater (*Table 5*).

Table 5 Cost of primary thrombolysis and primary surgery

	£	
	Thrombolysis	Surgery
Cost of radiology and surgical disposables*	407 (252–596)	82 (58–169)
Cost of radiology and surgical time*	441 (293–735)	562 (250–1300)
Total radiology and surgical cost*	861 (611–1244)	683 (309–1438)
Bed cost*	2189 (902–6020)	2497 (643–9115)
Total primary cost*	3230 (1543–8353)	3429 (1094–10 065)
Mean cost per limb salvaged	5124	13 167

*Values are median (10th centile range)

Discussion

These results show that a selective policy for managing acute limb ischaemia with a combination of primary thrombolysis and, where appropriate, primary surgery resulted in a cost to the hospital of approximately £3500 per patient. The study has also shown that high-dose bolus thrombolysis is more expensive but no more time consuming than low-dose therapy

The results may have been influenced by the small numbers involved, the heterogeneous nature of acute limb ischaemia, and the underlying pathology of the disease in each group. The high-dose bolus and low-dose infusion groups were well matched for many clinical features but a greater number required adjunctive surgery in the high-dose group. The need for surgery after thrombolysis and the prolonged hospital stay might reflect more severe disease in the high-dose group. If analysis of the present results is focused on the costs of the primary procedure, not subsequent surgery, then high-dose therapy was only £200 more expensive than low-dose infusion (the extra cost of opening a 50 mg rather than a 20 mg vial of tPA). The time that the radiology suite was occupied did not differ significantly between the groups.

In the second analysis, patients were selected by a protocol for managing acute limb ischaemia. They were not, therefore, comparable to those who required thrombolysis and so statistical analysis is not valid. The high mortality rate in the surgical group was consistent with that in other reports on the association of embolectomy and cardiac related death[4,5]. The early postoperative death of nine patients in the surgical group resulted in low bed occupancy and probably contributed to the low median cost of primary surgery. If this was a randomized study of surgery *versus* thrombolysis, the costs would be different.

The economics of acute limb ischaemia are complex and it is not surprising that there are few publications on the subject. One study in 1988[6] retrospectively reviewed 24 thrombolytic infusions with streptokinase and urokinase for a variety of anatomical lesions. Operating theatre and radiology room charges were similar but the disposable items used for thrombolysis were more expensive than those for surgery. Professional fees were included in the study, which gave the mean total cost per case of thrombolysis as $8232 compared with $8859 for 16 selected surgical procedures for similar lesions. Complete success was defined as successful thrombolysis not requiring surgery and therefore the mean cost at discharge for thrombolysis was four times that of surgery alone. More recently, a retrospective review[7] of 19 native arterial occlusions treated by thrombolysis and 29 treated by surgery noted that initial costs of the two treatments were similar but the mean cost per limb saved after thrombolysis was twice that of surgery ($45 171 *versus* $24 898). The explanation for the increased cost of thrombolysis was the greater number of adjunctive procedures (in 14 of 19 patients) and treatment of complications (in 12 of 19). These two retrospective studies support the results of the present study. The costs of primary surgery and thrombolysis were similar.

The largest comparison of costs of surgery and thrombolysis was presented as part of a randomized trial[1]. Median length of stay after thrombolysis or surgery was 11 days but the median total cost of thrombolysis was greater than that for surgery ($15 672 *versus* $12 253). The costs of the primary procedure were not given. The figures for hospital stay match the results in the present study, but total costs are not comparable because of the different patient groups. At an exchange rate of US $ 1·6 to the £1, the costs of thrombolysis and surgery in the USA are between two and three times higher than those in the UK.

This study has highlighted the difficulty in costing medical treatment[8]. It is one of the first to cost what has been thought of as a labour-intensive form of thrombolysis (high-dose bolus) with the established regimen of low-dose infusion. The study has shown no significant difference in the use or cost of radiological facilities between the methods, except for the cost of more tPA for the high-dose treatment. The major costs of thrombolysis are dependent on the need for surgical intervention for the underlying disease and complications of therapy. For successful and uneventful primary treatment the costs are similar for surgery and thrombolysis.

Acknowledgements

The authors thank B. Davies, D. Griffin and M. Squire for help in the preparation of this manuscript.

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British Journal of Surgery 1996, 83, 1394–1395

Still missing the boat with fatal pulmonary embolism

T. E. GILLIES, C. V. RUCKLEY and S. J. NIXON*

*Vascular Surgical Unit, University Department of Surgery, Royal Infirmary of Edinburgh and *Scottish Audit of Surgical Mortality, Royal College of Surgeons, Edinburgh, UK*

Correspondence to: Miss T. E. Gillies, Vascular Surgical Office, University Department of Surgery, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW, UK

Deaths from pulmonary embolism during 1994 among surgical inpatients in three Scottish regions were identified through the Scottish Audit of Surgical Mortality and reviewed to identify the risk factors for thromboembolic disease and the thromboprophylaxis received. Fifty-seven deaths were studied (3 per cent of total deaths); 25 (44 per cent) of the patients had received prophylaxis. Thirty-six patients were in a high-risk group, 19 were at moderate risk and two at low risk. Patients admitted as an emergency, those managed conservatively and those judged to be at moderate risk of thromboembolic disease were most likely not to have received thromboprophylaxis.

Thromboembolic prophylaxis by mechanical or pharmacological methods is effective in reducing the incidence of thromboembolic disease[1,2]. Despite this, the use of prophylaxis is not as widespread as might be wished. The National Confidential Enquiry into Perioperative Deaths highlighted the provision of thromboembolic prophylaxis as an area in which patient management could be improved[3].

The Scottish Audit of Surgical Mortality (SASM) is a national study, which examines every death among surgical inpatients in Scotland, excluding those due to terminal malignancy. This study set out to examine deaths reported to the SASM (excluding the Greater Glasgow regional office) during 1994, in which pulmonary embolism was given as the main cause of death, to assess the level of risk in each case for the development of thromboembolic disease and to identify the type, if any, of prophylaxis used. As the SASM examines deaths only among hospital inpatients, any deaths after discharge will not have been identified.

Patients and methods

A total of 1893 inpatient deaths were reported during 1994, and in 57 (3 per cent) pulmonary embolism was given as the major cause. The case notes were reviewed by a single observer (T.E.G.). Each patient was assigned to a risk group, high, moderate or low, according to the guidelines produced by the Thromboembolic Risk Factors (THRIFT) Consensus Group[2].

Deaths outwith the care of surgeons, non-fatal episodes of thromboembolic disease, deaths due to terminal malignancy and deaths at home following discharge have not been considered. The Aberdeen regional office is the only one to collect information on deaths among patients with orthopaedic trauma routinely.

Statistical analysis was carried out with a χ^2 test using Yates' correction factor for small sample size and Fisher's exact test as appropriate.

Results

Of the 57 patients who died, 18 were inpatients admitted for elective reasons and 39 had been admitted as an emergency. There were 28 women and 29 men of median (range) age 78 (28–93) and 76 (34–88) years respectively. The cause of death was determined by autopsy in 24 patients (42 per cent) and by clinical judgement and investigations in the remainder.

When divided according to the level of risk, 36 patients were at high risk, 19 at moderate risk and two at low risk. Operative intervention was undertaken in 41 patients (72 per cent) with a total of 45 procedures, 14 for malignant disease, 17 for benign disease, and orthopaedic or trauma surgery in 14. Conservative management was followed in 16 patients, seven of whom had malignancy (although none was terminally ill); median stay was 8 (range 1–47) days and 15 had an emergency admission.

A pharmacological, mechanical or a combination thromboprophylaxis regimen was followed in 25 patients (44 per cent). No patient had a contraindication to both mechanical and pharmacological methods of prophylaxis. In all cases pharmacological prophylaxis was commenced during the operative period. The provision of prophylaxis was significantly higher in the high-risk group (22 of 36 patients; corrected $\chi^2 = 8{\cdot}55$, 1 d.f., $P = 0{\cdot}003$) than in patients at moderate risk (three of 19). The use of thromboprophylaxis was lower in patients admitted as an emergency in both the high and moderate risk groups (*Fig. 1*). Only one of the 16 conservatively managed patients received any prophylaxis, although 15 were in the high or moderate risk categories.

There was no statistically significant difference in the use of prophylaxis between the orthopaedic patients and those treated within other specialties.

Paper accepted 2 July 1996

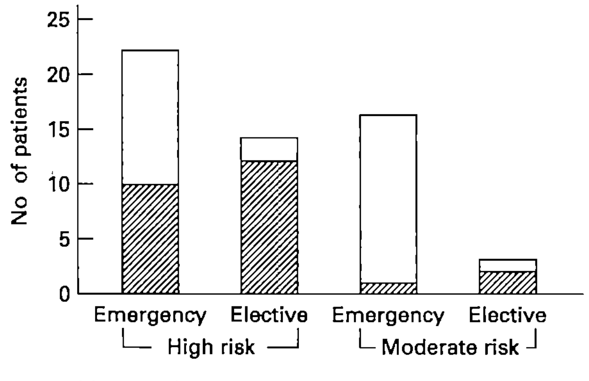

Fig. 1 Antithrombotic prophylaxis by mode of admission. □, No prophylaxis; ▨, received prophylaxis

Discussion

The true incidence of fatal pulmonary embolism is difficult to determine accurately. Without doubt, the number of deaths reported to this study is an underestimate of the perioperative mortality due to pulmonary embolism on account of the low autopsy rate, the nonspecific presentation in many patients and the fact that deaths following discharge were not included. In studies undertaken in countries such as Sweden, where autopsy rates are 75 per cent or more[4], a higher proportion of deaths (10 per cent) has been found to be due to fatal pulmonary embolism. Thromboembolic disease as a contributory or major cause of death will continue to be underdiagnosed in the UK as long as the autopsy rate remains low, and this hampers the development of any prospective study.

The effectiveness of thromboprophylaxis in preventing thromboembolic disease, fatal or otherwise, has been widely addressed. Although effective, it is not absolute in preventing disease, as evidenced by the 44 per cent of patients who died despite receiving prophylaxis.

Mechanical prophylaxis is often overlooked but has been shown to reduce the incidence of venous thromboembolism[5,6] in patients at moderate risk, although no conclusive reduction in the number of fatal pulmonary emboli has been demonstrated. However, stockings must fit accurately and are contraindicated in patients with peripheral arterial disease and/or diabetic neuropathy[7,8]. Intermittent pneumatic compression is a commonly used method, particularly during operation[9]. No mention of it has been made in this study because there was no record of it having been used in any case. It is possible that this was due to poor documentation rather than lack of use. Accurate documentation of the assessment of thromboembolic risk factors and the method of prophylaxis used is important for medicolegal purposes. This is not standard practice at present.

Three groups of patients have been identified from this study as less likely to receive adequate prophylaxis: patients admitted as an emergency, those at moderate risk and those managed without operation. If effective prophylaxis is to be given to all patients at risk, assessment must take place at the time of admission. Delay until the perioperative period omits those managed conservatively and is often overlooked in the emergency case. Better adherence to prophylactic policies would be facilitated by the use of structured clinical record forms into which a section on the assessment of the level of risk could be incorporated. Prophylaxis could then be prescribed according to the unit's preferred policy. A number of collaborative groups have produced guidelines[2,10] that could be used as a basis for local protocols.

Any study of fatal pulmonary embolism will be hampered by difficulties in collecting complete data from the large numbers of patients necessary, and there will remain some patients who die despite prophylaxis. This study has, however, demonstrated that there is still room for improvement in the provision of thromboembolic prophylaxis for surgical inpatients.

Acknowledgements

The assistance of Mrs Margaret Hunter, Mrs Wendy Ritchie and Mrs Moira Turner, the Audit Officers, is gratefully acknowledged The SASM is funded by the Clinical Research and Audit Group, Scottish Home and Health Department.

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British Journal of Surgery 1996, 83, 1396–1398

Prospective evaluation of dynamic contrast enhanced magnetic resonance imaging in the evaluation of fistula *in ano*

I. J. BECKINGHAM, J. A. SPENCER*, J. WARD*, G. W. DYKE, C. ADAMS and N. S. AMBROSE

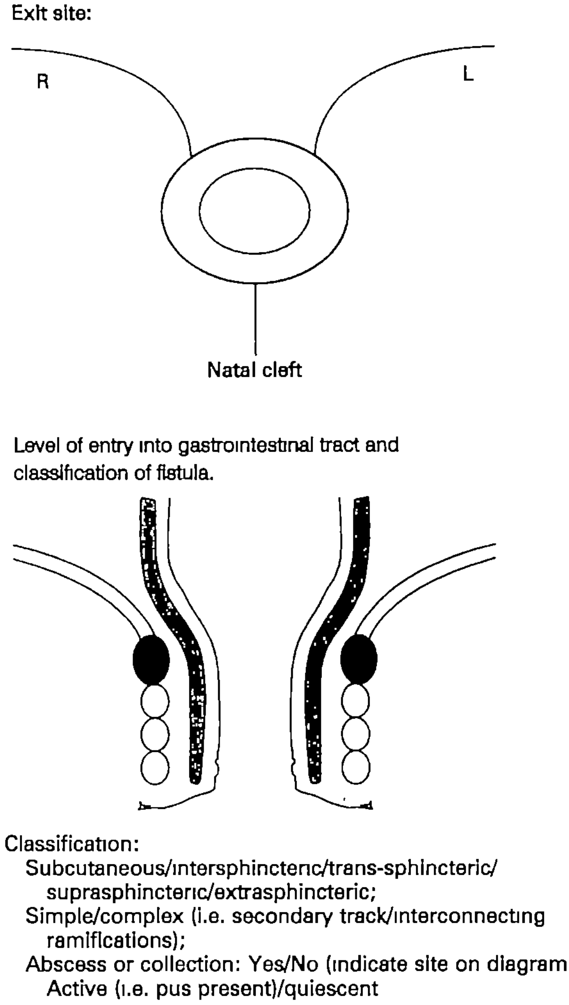
*Departments of Surgery and *Radiology, St James's Hospital, Leeds, UK*
Correspondence to: Mr I. J Beckingham, Derby City Hospital, Derby DE22 3NE, UK

Forty-two patients with a suspected diagnosis of fistula *in ano* underwent prospective comparison of digital rectal examination, dynamic contrast enhanced magnetic resonance imaging (DCEMRI) and surgical exploration. There were five discordancies: DCEMRI showed an ischiorectal abscess and track with no enteric connection in one patient who at operation was found to have a well epithelialized primary fistula. Four patients with fistulas on DCEMRI had no enteric opening found at surgery and were treated as having sinuses. Long-term follow-up has shown failure to heal in all patients and further surgery confirmed missed fistula. Compared with final outcome measures DCEMRI had a sensitivity of 97 per cent and specificity of 100 per cent in the detection of fistula. DCEMRI also identified more secondary tracks and was more accurate at identifying complex fistulas than either digital rectal examination alone or surgical exploration.

Fistula *in ano* is a relatively common condition occurring in approximately 1 in 10 000 individuals in the western world[1,2]. The key to the successful management of this condition lies in the correct identification of the fistula in relation to the anatomical structures through which it passes, and to the identification of additional tracks and abscesses which may prevent resolution of the treated primary fistula. While the majority of fistulas are simple and relatively easy to treat[3], those which cross the upper part of the external sphincter or are suprasphincteric or extrasphincteric are difficult to diagnose and pose a risk of incontinence from damage to the anal sphincters during exploration[4]. Missed internal openings or secondary tracks usually result in recurrent fistulas and additional surgery further increases the risk to continence. This prospective study was undertaken to compare the accuracy of digital rectal examination and surgical exploration with dynamic contrast enhanced magnetic resonance imaging (DCEMRI) in the assessment of fistula *in ano*.

Patients and methods

Forty-two consecutive patients referred to this hospital with a prospective diagnosis of fistula *in ano* between January 1994 and July 1995 were studied. There were 36 male patients, and an age range of 26–73 years. Two patients had Crohn's disease and two ulcerative colitis. Nine patients had undergone incision and drainage procedures for perianal or ischiorectal abscesses, and one patient with ulcerative colitis had an ileoanal pouch. Patients were seen initially in outpatient clinics and entered into the study, which involved digital rectal examination followed by magnetic resonance imaging (MRI) and definitive operation. Patients were classified as having no fistula (sinus, abscess, subcutaneous track), simple fistula (single track from skin to bowel) or complex fistula (more than one primary track, secondary tracks, horseshoe extensions or secondary abscesses). Findings were recorded on a standardized operation sheet by surgeons and radiologists (*Fig. 1*); cutaneous and enteric entry sites were noted and primary tracks classified as intersphincteric, trans-sphincteric, suprasphincteric or extrasphincteric according to Parks classification[5]. Neither surgeons nor radiologists were aware of each others' findings before performing their procedures.


Exit site:
R
L
Natal cleft
Level of entry into gastrointestinal tract and classification of fistula.

Classification:
- Subcutaneous/intersphincteric/trans-sphincteric/suprasphincteric/extrasphincteric;
- Simple/complex (i.e. secondary track/interconnecting ramifications);
- Abscess or collection: Yes/No (indicate site on diagram)
  - Active (i.e. pus present)/quiescent

Fig. 1 Fistula assessment sheet

Magnetic resonance imaging

MRI was performed with the patient in the supine position using a Siemens Magneton 42SP scanner (Siemens, Bracknell, UK). No bowel preparation or special equipment was required. Initial studies showed that the optimal sequences were SE T_2-weighted

Paper accepted 4 June 1996

axial (TE30,60/TR2000) followed by dynamic T_1-weighted TurboFLASH (flat low angle spin) axial and coronal (TE40/TR100/flip angle 80°) before and after enhancement with gadolinium. Gadolinium was administered as an intravenous bolus of 0·1 ml/kg and scans were taken at 10, 30 and 50 s after administration. The total scan took 20 min and was well tolerated by all patients in the study.

Digital assessment

Digital assessment was carried out by a consultant surgeon before surgery and within 7 days of MRI.

Operative findings

Sigmoidoscopy, proctoscopy and gentle probing of the fistula with a blunt-ended probe was performed, followed by surgical exploration by a consultant surgeon. Treatment included laying open of the fistula with removal of lining tissue, drainage of abscesses and fistulectomy. Setons were used in a number of patients. In patients who underwent more than one operation after developing further complications (e.g. failure of healing), information from the second or subsequent operation is included in the final outcome data and not in the initial surgical findings.

Follow-up

All digital and operative procedures were performed without previous knowledge of the MRI findings. Patients were followed until complete healing had occurred, and have been followed for a minimum of 6 months after complete healing. Data assessment sheets of the MRI findings were compared with those of the digital assessment and operative findings and subsequent follow-up.

Results

Primary fistula track

The presence and complexity of fistulas identified by each of the modalities are shown in *Table 1*. The number and type of fistulas according to Parks classification are shown in *Table 2*. DCEMRI identified nine patients without fistula, eight of whom were similarly diagnosed by digital examination and surgical exploration. Five had blind ending or superficial cutaneous tracks (three perianal hydradenitis, one perineal and one pilonidal sinus) and three others were confirmed to have no evidence of a track (one with severe colitis, one linear ulcer, one postanal canal repair). One patient was shown on DCEMRI to have extensive perianal inflammation and an ischiorectal abscess and track but no enteric connection could be seen. Digital examination and surgical exploration revealed a chronic epithelialized connection from the ischiorectal track to the left side of the dentate line. This was the only false-negative MRI result.

Of the 14 simple tracks seen by MRI, 13 were confirmed by digital examination and operation. In one patient shown on MRI to have a low posterior track entering the midline posteriorly, no enteric connection could be demonstrated at operation. This patient has continued to drain pus since operation.

Nineteen fistulas were classified as complex on DCEMRI by virtue of secondary tracks or abscesses. In three patients no enteric connection was identified by digital examination or surgery. In two there was extensive perianal sepsis and in the third patient fibrosis and scarring from previous surgery. All three patients have had continued suppuration despite drainage; two have undergone further surgery which has confirmed the presence of fistula openings at the site shown by DCEMRI. The third patient is awaiting further surgery.

Table 1 Presence and complexity of fistulas

	Digital examination	Surgery	DCEMRI	Final outcome
Simple	21	15	14	14
Complex	8	14	19	20

DCEMRI, dynamic contrast enhanced magnetic resonance imaging

Secondary tracks

Of the 21 fistulas classified as simple by digital examination five were found to be more complex at initial surgery and two more at subsequent procedures. In total DCEMRI identified seven horseshoe tracks, two of which were missed by digital examination, and six ischiorectal tracks, three of which were missed by digital examination. There were three high-level tracks, two suprasphincteric and one extrasphincteric, none of which were predicted by digital examination. One of the suprasphincteric tracks was found at operation but the two other high-level tracks were missed. Their presence was confirmed by continuing discharge and further surgery including laparotomy in the case of the extrasphincteric fistula in a patient with ulcerative colitis.

Discussion

A variety of radiological techniques has been tried to improve preoperative assessment of fistula *in ano* in an attempt to identify patients with complex fistulas and reduce the risk of recurrence. Contrast fistulography[6], endoanal ultrasonography[7] and computed tomography[8], have all been found to be less reliable than digital examination by an experienced surgeon in predicting the course and complexity of fistulas. The St Mark's Hospital study found non-enhanced MRI using STIR (short T_1 recovery time) fat suppression images to be comparable to digital examination and superior to endoanal ultrasonography[9,10]. STIR sequences without enhancement can provide high signals in old healed fibrotic tracks causing misleading interpretations and missed secondary

Table 2 Primary tracks (Parks classification)

	DCEMRI	Surgery	Final outcome
Intersphincteric	24	24‡	24
Trans-sphincteric	6*	4†	7
Suprasphincteric	2	1‡	2
Extrasphincteric	1	0§	1
No fistula	9	13	8

*Dynamic contrast enhanced magnetic resonance imaging (DCEMRI) missed one complex trans-sphincteric fistula; †surgical assessment missed three complex trans-sphincteric fistulas; ‡surgical exploration missed one simple intersphincteric fistula but diagnosed one suprasphincteric fistula as intersphinteric; §extrasphincteric fistula diagnosed surgically as a sinus

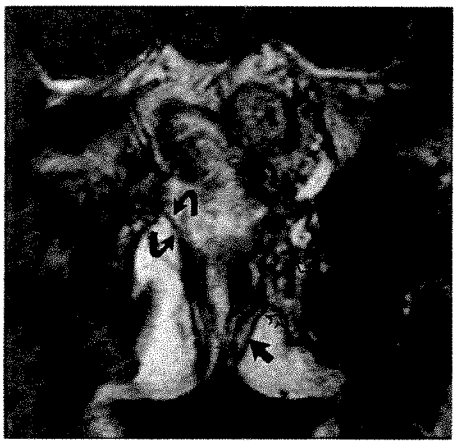


Fig. 2 Coronal plane dynamic contrast enhanced magnetic resonance images of the anal canal showing part of a trans-sphincteric fistula (solid arrow) with a secondary horseshoe abscess (hollow arrows). The pelvic floor is seen clearly on the patient's right side (curved arrows)

Table 3 Sensitivity and specificity of surgery and dynamic contrast enhanced magnetic resonance imaging

	DCEMRI	Surgery
True positive	33	30
False positive	0	0
True negative	8	8
False negative	1	4

Sensitivity and specificity for dynamic contrast enhanced magnetic resonance imaging (DCEMRI) were 97 and 100 per cent respectively, compared with 88 and 100 per cent for surgical exploration

features. In the present study gadolinium contrast was used to produce bright enhancement of active tracks and abscess cavities (*Fig. 2*) which were readily differentiated from the lower signal of old tracks. In addition to making primary tracks easier to identify, five patients had important findings shown only by contrast enhancement (two horseshoe tracks in patients thought to have simple fistulas and three discrete perianal abscesses not resolved from perianal inflammation on unenhanced images). In addition STIR sequences require a longer acquisition time resulting in a doubling of the total scan time.

There was one false-negative result with DCEMRI, which missed a chronic epithelialized track. DCEMRI produces contrast enhancement in granulation tissue which is not present in chronic epithelialized tracks. A similar false-negative result was seen in the St Mark's study[11] using non-enhanced STIR sequencing. However, both of these tracks were easily identified with digital examination alone and did not present diagnostic difficulty in the clinical setting.

The patient population from this unselected study represents a fairly typical group of patients presenting with fistula *in ano*. Studies comparing new techniques for investigation of fistula *in ano* have used surgical exploration as the 'gold standard' investigation with which to compare[7,9,10]. However, it is apparent from all these studies that surgery misses some fistulas since discharge continues after drainage of the 'sinus' or 'simple fistula'. A more accurate assessment of the ability of DCEMRI to predict fistula *in ano* is comparison with the results of surgical findings and the final outcome (including further operations). When this is used DCEMRI had a sensitivity of 97 per cent and specificity of 100 per cent for the correct prediction of a primary fistula track (*Table 3*). MRI was therefore superior to surgical assessment alone (sensitivity 88 per cent, specificity 100 per cent compared with final outcome) which may in part be accounted for by the limitations enforced on the surgeon when severe perianal inflammation may conceal a fistula opening and prevent identification of secondary tracks. Furthermore, the St Mark's studies[9–11], which demonstrated that digital examination was as good as MRI, may not be representative of experience in centres which see fewer complex cases of fistula *in ano*.

This study has shown that DCEMRI is superior to digital examination and surgical assessment in determining the position of the primary fistula track and the complexity of the fistula. Because the predictive value of digital examination to identify simple from complex fistulas in this mixed group of unselected patients was only 50 per cent, it is the authors' current policy to perform preoperative DCEMRI on patients with inflammatory bowel disease, non-healing after treatment of an apparently simple fistula or a recurrent fistula.

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British Journal of Surgery 1996, **83**, 1399

Short note

Role of the nurse endoscopist in colorectal practice

V. MOSHAKIS, R. RUBAN and G. WOOD

Colorectal Unit, Department of Surgery, George Eliot Hospital National Health Service Trust, College Street, Nuneaton CV10 7DJ, UK

Correspondence to: Mr V. Moshakis

Recent changes in the provision of colorectal services[1,2] have led the authors to train a nurse endoscopist in colorectal practice[3].

Methods

A registered general nurse was trained in flexible sigmoidoscopy and clinical coloproctology in accordance with an agreed protocol. The training took place during routine endoscopy lists in a medium-sized district general hospital. Under the direct supervision of a consultant (V.M.), the nurse (R.R.) was trained in the three main elements of colorectal endoscopy.

First, theoretical training covered the anatomy, physiology, pathology and clinical aspects of gastrointestinal disease, with special emphasis on the colorectum. Second, general endoscopy equipment training covered the mechanisms, cleaning and maintenance of flexible sigmoidoscopes; the principles and practice of infection control and the function and organization of endoscopy units were also taught. Third, flexible sigmoidoscopy training consisted of observation, performance of supervised procedures and postsigmoidoscopy management in 200 cases.

Fifty procedures were observed, during which continuous teaching of the clinical and technical aspects of endoscopy took place. The trainee then performed 50 supervised procedures. The first 25 were withdrawals and were part of colonoscopy in sedated patients. Following these, 50 flexible sigmoidoscopies were performed, with the trainer immediately available.

The nurse also learnt to use the proctoscope and to inject haemorrhoids, following the practice of the consultant to perform injection at the time of flexible sigmoidoscopy.

Assessment

Both the consultant trainer and pupil were assessed by an independent consultant gastroenterologist (G.W.)

Video recordings were made of 50 trainer and 50 pupil procedures. Data recorded included duration of procedure, depth of insertion, level of colon reached, quality of examination and diagnostic accuracy. The pupil performed 150 solo procedures in her training and assessment. The endoscopist was not identified on the pro forma or video recordings. The assessor scored each criterion and each procedure.

Scores for the pupil and trainer were totalled and compared. The pupil was considered able to perform competent and safe flexible sigmoidoscopy when her scores were equal to or within 15 per cent of those of the trainer.

Results

Total scores did not show any statistically significant difference between trainer and pupil. Quality and accuracy scores were all 94–97 per cent. Trainer and pupil achieved 60 cm insertion in similar numbers of cases (72 and 71 per cent), and reached the descending colon in one-half (50 and 49 per cent) of cases.

Competence in theoretical and endoscopy training was achieved in all areas with 'proficiency' marks awarded in all criteria in the training package.

No complication occurred throughout the training or the assessment.

Discussion

The training protocol was stricter and more thorough than the training of medical personnel recommended by the British Society of Gastroenterology. Assessment by a senior endoscopist not related to the training demonstrated objectively that the pupil had become as good or almost as good a sigmoidoscopist as the trainer. This assessment was based on scores in the main areas of technical skills and diagnostic accuracy.

It is recognized that the assessment is not completely objective. Review of a video recording is not quite representative of the real examination by the endoscope. In addition, the assessor reviewed the examinations without knowledge of the patients' history, so that diagnosis such as haemorrhoids or diverticular disease could be only subjective. Despite its limitations, this attempt objectively to prove the effectiveness of the training is the first such description in gastrointestinal endoscopic training.

A nurse can be taught to practise flexible sigmoidoscopy efficiently and safely. It is concluded that, with expert training and continuing education, the nurse endoscopist can become a vital resource in the colorectal team.

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Paper accepted 10 July 1996

British Journal of Surgery 1996, **83**, 1400

Short note

Disruption of the internal anal sphincter can occur after transanal stapling

R. FAROUK, P. J. DREW, G. S. DUTHIE,
P. W. R. LEE and J. R. T. MONSON
Academic Surgical Unit, University of Hull, Castle Hill Hospital, Cottingham, UK
Correspondence to: Mr R. Farouk, E6A, Section of Colon and Rectal Surgery, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55 905, USA

Disorders of continence are present in up to 60 per cent of all patients undergoing low anterior resection for rectal cancer[1]. This may be attributed to loss of rectal reservoir[2] with associated impairment of sensory function of the rectum or pelvic floor. Disruption of the anal sphincter complex may also contribute to postoperative continence disorders as a result of division of its innervation and/or anatomical disruption secondary to anal dilatation during transanal anastomosis[3]. Anal sphincter appearances have been studied prospectively by endoanal ultrasonography to determine whether such disruption occurs.

Patients and methods

Thirty-nine patients (18 women; median age 59 years) who underwent anterior resection with a stapled anastomosis for rectal cancer were assessed prospectively before operation, immediately after operation, and 3 months after surgery by endoanal ultrasonography (Bruel and Kjaer, Naerum, Denmark). Preoperative radiotherapy was not given to any of the patients assessed. Twenty-nine patients underwent a double-stapled anastomosis; the others had a purse-string suture inserted transabdominally followed by a transanal stapled anastomosis. The size of the stapling gun used was 29 mm (27 patients), 31 mm (eight) and 28 mm (four).

Results

No internal sphincter defects were observed before operation. External anal sphincter defects were found in three female patients with a previous obstetric history.

Seven patients were observed to have defects of the internal sphincter immediately after stapling; in one a 29-mm stapling gun had been used and in six a 31-mm device. All of these patients had undergone double stapling. These defects were present 3 months after surgery. Three patients had disruption of the entire length of the internal sphincter at one site (*Fig. 1*), three had 50 per cent disruption of the proximal internal sphincter, and one patient had two sites of disruption affecting 50 per cent of the length of the internal sphincter. Five of the seven patients with internal sphincter defects are incontinent of solid stool on more than two occasions per week after a median of 4 (range 3–7) months' follow-up. The remaining two patients still have a defunctioning ileostomy. There were no additional defects in the external sphincter after surgery.

Paper accepted 31 May 1996

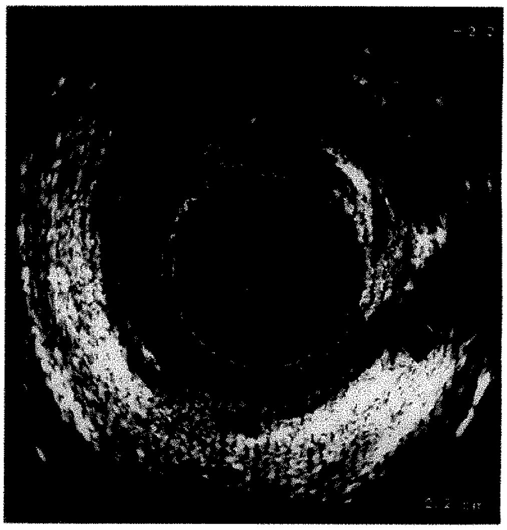

Fig. 1 Endoanal scan revealing complete disruption of the internal sphincter 3 months after low anterior resection completed by a double-stapled anastomosis. The hypoechoic ring of the internal sphincter has been divided and the cut ends of the internal sphincter have retracted (arrows)

Discussion

Up to 43 per cent of patients achieve perfect postoperative continence 5 years after coloanal anastomosis[4]. Of the remaining patients, 34 per cent have 'acceptable' continence with fewer than two episodes of faecal incontinence per week. The remaining patients have more frequent episodes of incontinence requiring daily use of pads[4].

In this study, seven of 39 patients had evidence of internal anal sphincter disruption immediately after a transanal stapling procedure. These defects persisted at 3 months' follow-up. The defects were associated primarily with the use of the larger diameter stapling guns. Similar defects of the internal sphincter have been observed previously by endoanal ultrasonography after ileal pouch–anal anastomosis[5]. Patients with these defects have frequent episodes of faecal incontinence in the early postoperative period.

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British Journal of Surgery 1996, **83**, 1401–1405

Disconnection, pouch revision and reconnection of the ileal pouch–anal anastomosis

P. M. SAGAR, R. R. DOZOIS, B. G. WOLFF and K. A. KELLY

Division of Colon and Rectal Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA
Correspondence to: Dr R. R. Dozois, Division of Colon and Rectal Surgery, Mayo Clinic, 200 1st Street SW, Rochester MN 55 905, USA

The aim of this retrospective study was to determine the outcome of patients with a dysfunctional pelvic ileal reservoir in whom disconnection of an ileal pouch–anal anastomosis (IPAA), pouch revision and reanastomosis had been carried out. There were 23 patients (15 women). At the revision operation functional problems were found to be due to a long efferent spout (nine patients), sepsis and/or fistula (four), a redundant blind limb (three), a twisted pouch (three), anastomotic problems (three) or no reservoir (one). The pouch was salvaged in 16 patients and a new pouch was constructed in seven. The pouch–anal anastomosis was resutured in 22 patients and stapled in one. Postoperative complications (all minor) occurred in six patients. Two patients underwent two revisions of IPAA. At a median follow-up of 5 (range 1–10) years, 11 patients reported good to excellent function, five reported fair function and one reported recurrent pouchitis. Revision surgery was unsuccessful in six of 23 patients (three had gross incontinence, two excessive bowel movements and one Crohn's disease), and they subsequently underwent pouch excision. It is concluded that revision of an ileal reservoir and IPAA can be undertaken safely with good results in carefully selected patients.

Ileal pouch–anal anastomosis (IPAA) is well established as the principal elective operation for most patients with chronic ulcerative colitis and familial adenomatous polyposis. As experience has been gained, the procedure has been refined. Since the early descriptions[1], modifications have included the incorporation of an ileal pouch[2], different designs of the pouch[3], reduction in the extent of rectal mucosectomy[4], use of stapling instruments and less manipulation of the anal sphincter. The operation is safe but complex. The incidence of postoperative complications is 30–50 per cent and is related mainly to the experience of the surgical team[4]. The success rate is 95 per cent and the quality of life is usually good[5].

A small subset of patients exists in whom the long-term functional result is poor. Although in many of these cases the problem may be related to recurrent episodes of pouchitis or postoperative pelvic sepsis[6], some patients may benefit from surgical intervention.

The aim of this study was to review patients with an unsatisfactory outcome after IPAA in whom the anastomosis had been taken down, revision surgery had been performed on the pouch and the IPAA reconstructed. The hypothesis was that, in carefully selected patients, such surgical intervention could be achieved safely and with good long-term results.

Patients and methods

Between January 1981 and December 1995 more than 1700 patients underwent IPAA at the Mayo Clinic. Twenty-three patients (15 women) had repeat IPAA with disconnection of the anastomosis, revision of the pouch and repeat IPAA. Most of these patients (19 of 23) had the original anastomosis at other centres. Two patients underwent this repeat procedure twice. The details of the patients are shown in *Table 1*.

An IPAA registry has been maintained to record demographic details, mode of presentation, operative procedure, type of ileal pouch, use of diverting ileostomy and postoperative complications. Preoperative and postoperative data are also recorded and each patient completes a functional questionnaire annually. The questionnaire documents the number of daily and nocturnal bowel movements, daytime and night-time continence with the need to wear a pad, perianal irritation, ability to discriminate flatus from faeces and use of medication.

Table 1 Patient details

No. of patients	23
Sex ratio (M:F)	8:15
Median (range) age (years)	31 (13–55)
Preoperative diagnosis	
Chronic ulcerative colitis	21
Chronic ulcerative colitis with dysplasia	1
Familial adenomatous polyposis	1
Original pouch design	
Single lumen	1
J pouch	13
H pouch*	4
S pouch	4
U pouch†	1
Ileal pouch–anal anastomosis	
Hand sewn	22
Double stapled	1

*Fonkalsrud or lateral ileal reservoir. †This patient had effectively had a J pouch constructed and then placed upstream from the terminal ileum, which was then anastomosed to the anal canal; the terminal ileum thus acted as an efferent spout from the J pouch

Patients who presented with pouch dysfunction underwent standard investigations with inspection and palpation of the IPAA, stool culture, pouchoscopy and multiple biopsies, water-soluble contrast enema, manometry of anal sphincter and pouch, and a small-bowel contrast study if Crohn's disease was suspected.

The notes and registry data of each of the 23 patients were reviewed. As follow-up of all patients on the registry continues prospectively, outcome was determined in every patient. The study was approved by the Mayo Institutional Review Board.

Surgical technique

The patient was placed with the legs elevated in Lloyd-Davies supports. The abdomen was opened and the ileal pouch was

Paper accepted 8 July 1996

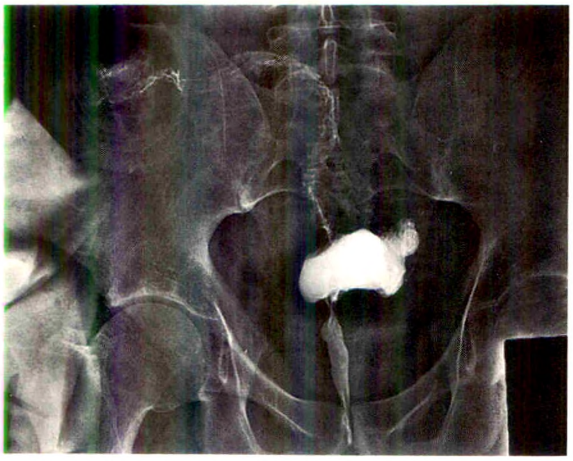

Fig. 1 Water-soluble contrast enema in a patient with a Fonkalsrud (H) pouch. The pouch lies almost transversely in the pelvis and the efferent spout is too long

identified and dissected out with a combination of electrocautery and sharp dissection. When the IPAA had been identified from above, perineal dissection was used to disconnect the anastomosis, and the pouch was delivered out of the abdomen. The pouch was revised according to the nature of the problem. This included excision of a long efferent spout with or without excision of the original pouch (*Fig. 1*), excision of the original pouch with construction of a new pouch, excision of a long blind end (*Fig. 2*), rotation of the pouch on its longitudinal axis and excision of fistulous tracts with repair of the pouch (*Table 2*). The new pouch was then anastomosed to the anal canal. Four anchoring sutures were placed into the walls of the pouch and the levator muscles, and then a series of interrupted absorbable sutures was placed between the pouch and the anal mucosa. The procedure was covered with a diverting ileostomy in all cases. Intestinal continuity was restored 2–3 months later after a water-soluble contrast study had demonstrated satisfactory healing.

Results

Morbidity and mortality

There were no deaths. Postoperative complications developed in six of 23 patients. Five patients developed partial small bowel obstruction, all of which resolved without operation; one patient developed a significant cardiac arrhythmia (junctional rhythm) during operation. The median length of stay in hospital was 10 (range 6–17) days. The ileostomy was closed uneventfully in each patient 8–14 weeks later.

Causes of pouch dysfunction

Nine patients were found to have an excessively long efferent spout (5–11 cm). Four patients had pelvic sepsis and/or fistulas. Three patients had a long mobile blind limb capable of obstructing outflow from the pouch (*Fig. 2*). Three patients were found to have rotated pouches, in one of whom bowel proximal to the pouch had been intussuscepted within the pouch and sutured (presumably accidentally) to the IPAA such that the pouch itself was excluded from the flow of intestinal content. Problems specific to the IPAA included partial separation (one patient), residual disease after a double-stapled anastomosis (one) and a long stenosis (one). Finally, one patient had undergone ileoanal anastomosis with no reservoir.

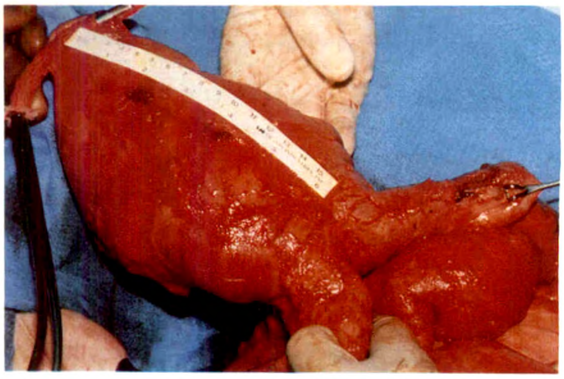

Fig. 2 The blind end of the pouch is long and free to move. As the lower part of this pouch and the blind end filled with stool, the blind limb occluded the upper part of the pouch. Defaecation was difficult and incomplete

Table 2 Indication for reoperation and outcome in 23 patients

Problem	No. of patients	Treatment	Outcome
Long efferent spout	9	New pouch (5) Revised pouch (4)	Success in seven
Sepsis and/or fistula	4	Revised pouch	Success in two
Blind limb	3	Revised pouch	Success in one
Twisted pouch	3	New pouch (1) Old pouch retained (2)	Success in three
IPAA	3	Old pouch retained	Success in three
No pouch	1	New pouch	Success

IPAA, ileal pouch–anal anastomosis

Functional outcome

The eventual outcome of the patients after a median follow-up of 5 (range 1–10) years is shown in *Table 2*. Attempts to salvage the pouch and obtain satisfactory function failed in six of 23 patients. Failure was due to gross faecal incontinence in three patients, excessive frequency of bowel movements in two and unrecognized Crohn's disease in one. The other 17 patients have fair to excellent pouch function with a median frequency of bowel movements of 5 (range 2–11) per 24 h and 1 (range 0–2) at night. Thirteen of the 17 patients are able to discriminate confidently between flatus and faeces such that they are able to pass gas without the need to visit the toilet. Seven patients have perianal irritation, four have occasional faecal seepage (less than once a week) and two need to wear a perianal pad most of the time. Five patients still require antidiarrhoeal medication and two have recurrent episodes of confirmed pouchitis. All these patients are pleased to have opted for repeat IPAA rather than excision of the pouch with permanent ileostomy.

Discussion

As the operation of IPAA has become more widespread, a number of patients have been referred with compli-

Table 3 Complete reconstruction of the ileal pouch–anal anastomosis

Reference	Year	No. of patients	Problem	Outcome
Liljeqvist and Lindquist[8]	1985	7	Long spout	Good function in five patients; two failures
Poggliolí *et al.*[9]	1993	6	Twisted pouch (1) Afferent limb stricture (1) Pouch–urethral fistula (1) Pelvic sepsis (1) Ischaemic pouch (1) Outflow obstruction (1)	Good function in four patients; pouch excised in one and stoma not closed in one
Nicholls and Gilbert[10]	1990	6	Long spout	Good function in four patients; two self-catheterize
Fazio and Tjandra[11]	1994	2	Residual disease, dysplasia	Good function in both patients

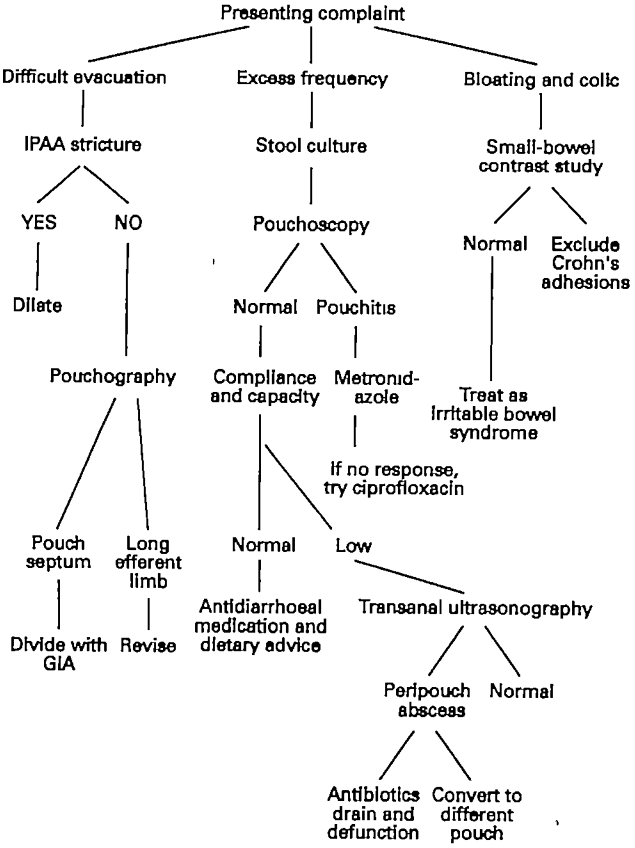

Fig. 3 Investigation of pouch dysfunction. IPAA, ileal pouch–anal anastomosis. GIA (US Surgical, Norwalk, Connecticut, USA)

cations related specifically to the function of the pouch. Many respond to conservative treatment, but some cases are resistant and reoperation may be necessary. Reoperation may involve dilatation of the anastomosis, drainage of perianastomotic abscesses, unroofing of anastomotic sinuses, placement of setons or fistulotomy, or re-establishment of a diverting ileostomy[7]. In a small group of patients, however, these relatively simple procedures are not indicated and disconnection of the IPAA, revision or reconstruction of the pouch and a second IPAA is required (*Table 3*). This study has demonstrated that with careful selection this can be accomplished safely with good functional results in the majority of patients.

Investigation

The selection of patients is crucial. *Fig. 3* shows an algorithm of the investigation of these patients. A water-soluble contrast enema and poor clearance of contrast at the time of defaecating proctography may identify a long efferent spout. The algorithm for patients with excessive frequency of bowel movements is designed to identify non-surgical causes such as infection and pouchitis. Nevertheless, some of these patients may have inadequate evacuation which manifests itself as excessive frequency. A final subset of patients complain of bloating and colic. Although some may have adhesions or Crohn's disease, most seem to have a variant of irritable bowel syndrome and are best referred back to their physician.

Long efferent spout

When the S pouch was first described, a long efferent ileal limb was incorporated in the design to reduce the risk of faecal incontinence[2]. It was later realized that this was both unnecessary and troublesome, because it was associated with incomplete or difficult evacuation, with up to 50 per cent of patients requiring self-catheterization[12]. Although attempts have been made to excise the limb and reanastomose the pouch to the anus by a transanal approach, a transabdominal approach seems to offer the best chance of success[10]. Although the long efferent spout was the main cause of the problem in this subset of nine patients in the present study, coexistent stenosis at the junction between the pouch and spout (which may be acutely angulated) or the spout–anal anastomosis was also apparent to a variable degree. At operation the aim was to excise the spout in its entirety and establish an anastomosis between the most dependent part of the pouch and the anal canal. The original pouch was preserved where possible. The original operative notes often referred to difficulty in obtaining sufficient length to form a tension-free anastomosis. Interestingly, this was never a problem with the repeat operations, presumably because of lengthening of the mesentery in the interim. All patients in the present series were able to evacuate spontaneously after excision of the efferent spout.

Pelvic sepsis and pouch–cutaneous fistula

The rate of pelvic sepsis after IPAA ranges from 0 to 25 per cent[6,13,14]. This rate declines with experience[7] and with use of shorter rectal cuffs[15]. Pelvic sepsis is widely regarded as a major cause of pouch dysfunction. The policy at the Mayo Clinic has been to excise pouches in which the functional result is poor as a consequence of serious pelvic infection. In the present series, pelvic sepsis was the underlying problem in only three patients, two of whom had two attempts at repeating the IPAA. The literature is devoid of any convincing series of successful repeat IPAA after 'true' pelvic sepsis.

One patient had a pouch-cutaneous fistula without sepsis. Complex fistulas that present late suggest hitherto unsuspected Crohn's disease. The presence of a controlled pouch-abdominal wall fistula (without abscess cavity) may warrant revisional IPAA but a stiff, inelastic, ileal pouch that has become fibrotic secondary to sepsis acts as a conduit rather than a reservoir and is best excised.

Separation of the ileal pouch-anal anastomosis

Separation of the IPAA was the reason for repeat IPAA in only one patient. This is, however, not an uncommon postoperative complication and occurs in up to 22 per cent of patients[14,16,17]. It is more common with a hand-sewn than with a stapled anastomosis[18] and is associated with severe gross rectal inflammation with difficult mucosectomy and long rectal cuffs[15]. The majority will either heal spontaneously or respond to operative drainage of associated abscesses, unroofing of anastomotic sinuses or transanal repair of the dehiscence and delayed closure of the ileostomy[7].

Anastomotic stricture

Excessive tension on the IPAA with ischaemia may lead to anastomotic stricture. This is compounded in the presence of perianastomotic sepsis with subsequent fibrosis. A soft stricture is often evident at the time of closure of the ileostomy, which yields to gentle dilatation, and most strictures seen subsequently can be dilated in the surgery. When an anastomotic stricture responds to dilatation, the eventual functional outcome is no different to that of patients without a stricture[19]. A long or tortuous stricture will not respond so easily and repeated attempts at dilatation may aggravate the problem. In such cases, complete revision of the IPAA may be beneficial.

Retained rectal mucosa

Concerns about the possibility of damage to the anal sphincter during transanal mucosectomy led to the development of the double-stapled IPAA in which the anorectum is transected after application of a linear stapler to the top of the anal columns and the use of a circular stapler placed into the anal stump to construct the IPAA. A number of authors have reported a variable length of rectal mucosa left *in situ* as the direct result of this technique. Although only one patient in the present series underwent repeat IPAA because of recurrent symptoms from the residual diseased mucosa, it seems likely that, as the double-stapled technique becomes more popular, more and more patients will require revision surgery because of inadequate eradication of disease at the time of the original operation. Dysplastic change within remnants of rectal mucosa has also been described[11]. Transanal mucosectomy with ileal pouch advancement and neoileoanal anastomosis has been described in two patients[11]. The technique is similar to that employed for the treatment of complex pouch-anal fistula[20].

Outcome

Postoperative morbidity was encouragingly low despite the complex nature of these repeat procedures. Anal sphincter function was also good despite the second attempt at IPAA. Great care was taken in each case, however, to identify the sphincter and dissect cautiously in the plane between any residual mucosa and the muscle. Six of the 17 patients with successful operations continue to experience less than perfect continence with occasional seepage (four patients) or the need to wear a pad (two). Even these patients are more than satisfied with the functional outcome.

In conclusion, disconnection, pouch revision and repeat IPAA can be accomplished safely with a good prospect of success. The indications for surgery can be summarized as poor initial surgical technique and problems of a 'mechanical' nature, while sepsis (and Crohn's disease) appear to be the major contraindications.

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British Journal of Surgery 1996, 83, 1406

Short note

Low malignant potential of the double-stapled ileal pouch–anal anastomosis

P. N. HARAY, B. AMARNATH, E. G. WEISS, J. J. NOGUERAS and S. D. WEXNER

Department of Colorectal Surgery, Cleveland Clinic Florida, 3000 West Cypress Creek Road, Fort Lauderdale, Florida 33309-1743, USA

Correspondence to: Dr S. D. Wexner

The operative treatment of ulcerative colitis has changed with the development of the stapled technique of pouch construction and the procedure of double-stapled ileal pouch–anal anastomosis (IPAA). This technique is being used at many specialist centres as the procedure of choice for restorative proctocolectomy (RPC) for ulcerative colitis because of its many advantages, including a shorter operating time, a comparatively easier technique owing to the omission of the mucosectomy, a lower rate of pelvic sepsis and also some evidence that the reduced anal manipulation and preservation of the anal transitional zone mucosa lead to a better functional outcome. However, the major theoretical disadvantage of this technique is the possible development of dysplasia and eventually carcinoma in the retained mucosa. The aim of this study was to evaluate this risk of dysplasia in the retained anal mucosa in patients with ulcerative colitis who underwent RPC with a double-stapled IPAA without mucosectomy.

Patients and methods

The records of 109 patients who underwent RPC with non-mucosectomy double-stapled IPAA for ulcerative colitis from September 1988 to December 1993 were reviewed. A minimum follow-up of 1 year was obtained. Patients who had IPAA for any condition other than ulcerative colitis were excluded, as were those with ulcerative colitis who were found to have carcinoma or dysplasia in the colon at the time of surgery. The histology of the distal rectal doughnut as well as the follow-up biopsies were reviewed by one of two pathologists. Follow-up studies included clinical evaluation with digital examination, endoscopy and random 2-mm pinch biopsies of the retained mucosal cuff. These biopsies were undertaken at the time of ileostomy closure and then annually, and any dysplasia was noted and graded. If the doughnut and two consecutive biopsies revealed squamous epithelium, further follow-up biopsies were not performed.

Results

There were 69 men (mean age 42·5 (range 14–72) years) and 40 women (mean age 37·5 (range 23–71) years). A total of 109 rectal doughnuts were reviewed. During follow-up of 1–6 (mean 2·6) years, a total of 186 biopsies of the anal mucosa were examined (mean 1·7 follow-up biopsies per patient; all patients had at least one biopsy). Only one patient was noted to have low-grade dysplasia in the distal rectal doughnut at the time of operation. Four follow-up biopsies of the retained mucosa in this patient over a period of 3 years, however, revealed no evidence of dysplasia. There was no recorded case of dysplasia in the follow-up biopsies of the retained mucosa in any patient in the series. No carcinomas were noted, either at the time of surgery or during the follow-up period.

Discussion

Double-stapled IPAA has become the procedure of choice in patients with ulcerative colitis after RPC. Ambroze *et al.*[1] have questioned the advisability of non-mucosectomy ileoanal reservoir because of the potential for malignant change in the retained mucosa. However, there have been no reports of carcinoma in the retained mucosal strip. Conversely, there have been several reports of viable rectal mucosa following mucosectomy[2]. The only major difference with respect to the risk of malignant disease is that, after mucosectomy, surveillance is difficult, while double-stapled IPAA without mucosectomy affords an opportunity to survey the mucosa regularly with visualization, palpation and biopsy[3]. Low-grade dysplasia in the distal rectal doughnut at the time of the original operation was noted in only one of 109 patients in this series. No dysplastic change was noted in any of the follow-up biopsies. Tsunoda *et al.*[4] reported a series of 118 patients with ulcerative colitis who underwent RPC: 110 had no carcinoma or dysplasia in the colectomy specimen. In this group, dysplasia was seen in the mucosal strippings of only one patient. This 0·9 per cent incidence is exactly the same as that noted in the present series. Ziv *et al.*[5] have reported a series of 254 patients who underwent non-mucosectomy stapled IPAA with a similar incidence of proven dysplasia of only 0·8 per cent. Schmitt *et al.*[3], in an earlier series from this department, reported on the first 51 patients (who are included in the present study) and found no dysplasia in any patient, either at the time of initial surgery or during a mean follow-up of 8·6 months. It appears, therefore, that the risk of malignant transformation in the strip of retained anorectal mucosa is slight and does not increase appreciably in the first few years after operation. The procedure of double-stapled IPAA without mucosectomy for patients with ulcerative colitis is quite safe.

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Presented to the annual meeting of the Association of Surgeons of Great Britain and Ireland, Glasgow, May 1996
Paper accepted 29 June 1996

British Journal of Surgery 1996, 83, 1407–1412

Sequential systemic platelet-activating factor and interleukin 8 primes neutrophils in patients with trauma at risk of multiple organ failure

A. J. BOTHA, F. A. MOORE, E. E. MOORE, V. M. PETERSON, C. C. SILLIMAN and A. W. GOODE

Department of Surgery, Denver General Hospital, University of Colorado Health Sciences Center, Denver, Colorado, USA
Correspondence to: Mr A. J. Botha, Department of Surgery, Middlesex Hospital, Mortimer Street, London W1N 8AA, UK

Plasma from 33 patients at risk of multiple organ failure (MOF) after major trauma was tested for a priming effect on neutrophils, and for the presence of platelet-activating factor (PAF) activity and interleukin (IL) 8. Plasma sampled at 3, 6, 12 and 24 h after injury significantly primed normal neutrophils to release mean(s.e.m.) 1·26(0·19), 1·33(0·26), 1·04(0·14) and 0·86(0·13) nmol superoxide per min per $1{\cdot}3 \times 10^6$ neutrophils respectively ($P < 0{\cdot}05$). Priming at 3 h after injury was inhibited by mean(s.e.m.) 63·8(7·0) per cent by the PAF antagonist, WEB 2170 ($P < 0{\cdot}01$). Mean(s.e.m.) plasma IL-8 was raised at 6 and 12 h after injury to 785(183) and 836(175) pg/ml ($P < 0{\cdot}01$). At 12 h after injury the plasma IL-8 level correlated directly with the number of units of red blood cells transfused ($r = 0{\cdot}64$, $P < 0{\cdot}01$), and was significantly higher in the group of six patients who developed MOF ($P < 0{\cdot}05$). These data suggest that after trauma the mediators PAF and IL-8 appear sequentially in the circulation, are potential mechanisms of circulating neutrophil priming, and that IL-8 may also be an early biochemical marker predicting the onset of MOF.

Polymorphonuclear neutrophils are important effector cells in the systemic inflammatory response syndrome, a premonitor of multiple organ failure (MOF)[1,2]. Priming of neutrophil adhesion and superoxide generation are prerequisites for neutrophil sequestration and tissue injury[3,4]. Previous studies have revealed that circulating neutrophils are endogenously primed for enhanced superoxide anion release and β_2-integrin expression within hours after a major injury[4,5]. The first 24 h after trauma is therefore a vulnerable window for neutrophil-mediated end-organ injury, especially when these primed and sequestered neutrophils are subjected to an activating stimulus. However, little is known about the kinetics and mechanisms of neutrophil priming during this vulnerable period.

In contrast to 'flow' phase catabolic changes after injury that are caused by stress hormones, 'ebb' or acute phase changes are thought to be due to specific mediators, which include platelet-activating factor (PAF), eicosanoids and cytokines[6–8]. PAF and the cytokine interleukin (IL) 8 are particularly important because of their priming effect on neutrophils and their potential role in the development of a systemic inflammatory response and MOF[7,9–11]. *In vitro* experiments have shown both PAF and IL-8 to be potent and rapid primers of neutrophil superoxide release[4,12,13]. During intestinal ischaemia–reperfusion in a rat model, designed to mimic the splanchnic hypoperfusion experienced after major trauma, there is a fivefold increase in PAF in the gut mucosa and portal blood, and circulating PAF has been implicated in causing both neutrophil priming and the systemic shock response[9,14–16]. In addition to endogenous PAF production, PAF-like lipids are also found in large quantities in transfused blood products[17,18]. Blood products also contain substantial amounts of cytokines such as IL-6 and IL-8[19,20]. In addition, cytokines are produced endogenously by several cell lines after injury[10]. The kinetics of systemic release of PAF and IL-8 after injury have not been studied, but in a human blister fluid model of local skin trauma, expression of PAF-like lipids preceded IL-8 by several hours, suggesting a sequential release of lipid and cytokine mediators after injury[21].

Victims of major trauma suffer mechanical tissue injury and ischaemia–reperfusion injury due to shock, as well as receive substantial transfusion of blood products. This study was therefore designed to investigate whether plasma from patients with major trauma contains mediators that prime neutrophils, whether PAF activity in the plasma precedes IL-8, and whether PAF activity and/or IL-8 levels are increased in patients who ultimately develop MOF.

Patients and methods

In a previous epidemiological study, age greater than 55 years, Injury Severity Score (ISS) above 25 and a transfusion requirement of more than 6 units of red blood cells within the first 12 h of injury, were identified as independent risk factors for the development of MOF[22]. For this laboratory study, between April 1993 and August 1994, only patients (1) aged between 18 and 55 years, (2) who had major trauma to the torso requiring a laparotomy within the first 3 h of admission, and (3) who had an ISS of 25 or more, or an ISS above 15 associated with transfusion of 6 or more units of blood within the first 12 h, were included. Patients with pre-existing organ dysfunction or major head injury (i e with a Glasgow Coma Scale (GCS) score below 8) were excluded. From day 3 after trauma, pulmonary, renal, hepatic and cardiac function were graded daily using a clinical and laboratory based scoring system from 1 to 4 for each organ. MOF is defined as a total organ dysfunction score greater than or equal to 4, with two or more dysfunctional organs[22]. Demographic, risk factor and outcome variables were collected and included: (1) host factors (sex, age, pre-existing disease); (2) tissue injury (ISS, GCS); (3) clinical signs of ischaemia–reperfusion (judged from systolic blood pressure in the emergency department, red blood cell transfusion within the first 12 h of injury, serial blood lactate levels and base deficit); and (4) outcome (septic and non-septic complications, duration of mechanical ventilation, length of stay on the surgical intensive care unit (ICU), MOF, death). Written informed consent was

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Presented to the Surgical Forum of the American College of Surgeons in Chicago, Illinois, USA, October 1994 and the Surgical Research Society in London, UK, January 1995
Paper accepted 6 June 1996

obtained from all patients, or next of kin, before enrolment. Ten healthy adult volunteers served as normal controls.

Plasma priming

Blood sampling. Central venous blood from patients and peripheral venous blood from volunteers was collected in chilled tubes containing ethylenediamine tetra-acetic acid and immediately centrifuged at 1000*g*. The plasma was stored at −70°C and thawed to 37°C only once before use in experiments. Normal neutrophils were obtained by sampling peripheral blood from healthy volunteers in heparinized glass tubes at room temperature.

Separation of neutrophils Slight modifications of the original technique described by Boyum *et al.*[23] were employed. Briefly, heparinized blood was layered over a sodium metrizoate/Dextran 500 solution (PMN; Robbins Scientific Corporation, Sunnyvale, California, USA) and centrifuged at 400*g* for 30 min at room temperature. Contaminating erythrocytes were removed by hypotonic lysis, and neutrophils were washed twice in 0·9 per cent sodium chloride and resuspended in 0·1 per cent dextrose in Dulbecco's phosphate-buffered salt solution (Cellgro; Mediatech, Herndon, Virginia, USA). Purity and viability (tested by trypan blue dye exclusion) of neutrophil preparations were above 95 per cent

Incubation time Plasma obtained in the first 24 h after injury from the first four patients was used to determine the shortest incubation time in which plasma would prime neutrophils. Priming was defined as enhanced neutrophil superoxide release after stimulation with *N*-formyl-methyl-leucyl-phenylalanine (fMLP). Neutrophils from volunteers were suspended in buffer and incubated for 5, 15, 30 and 60 min in an equal volume of patient plasma at a final concentration of 1×10^7 neutrophils/ml). After incubation, aliquots of the mixture were transferred to a microplate and neutrophil priming for superoxide release assessed

Measurement of superoxide anion release Extracellular release of superoxide was measured using a THERMOmax microplate reader supported by SOFTmax software (Molecular Devices, Menlo Park, California, USA) as described previously[4]. Ferricytochrome c, superoxide dismutase (SOD) and fMLP were purchased from Sigma Chemical Company, St Louis, Missouri, USA. Each assay of neutrophil superoxide production was performed in duplicate microtitre plates that contained $1 \cdot 3 \times 10^6$ neutrophils/ml (i.e. 2×10^5 cells/well) and ferricytochrome c 75 μmol/l in a final volume of 150 μl. In addition, SOD 100 μg/ml was added to the reaction mixture of a third well to measure SOD-inhibitable ferricytochrome c reduction. Neutrophils were kept in suspension by automated shaking of the microtitre plate just before each spectrophotometric reading. Dual beam spectroscopy at 550 nm and 450 nm commenced on addition of fMLP 1 μmol/l. Readings continued every 20 s for 10 min. The reaction mixture was maintained at 37°C, and data were plotted kinetically as the maximum velocity (V_{max}) of the reaction V_{max} was calculated for five readings and expressed as a change in optical density per minute An extinction coefficient of 8400 l/mol for ferricytochrome c (path length 0·4 cm) was used to convert V_{max} results to nmol superoxide per min per $1 \cdot 3 \times 10^6$ neutrophils.

Time course after injury Neutrophils from volunteers were incubated for 5 min in heterologous control plasma, as well as plasma sampled from the first 22 patients at 3, 6, 12, 24, 48, 72, 96 and 120 h after injury. Neutrophil priming was measured thereafter as described above.

WEB 2170 inhibition of plasma priming. To test whether the priming of healthy control neutrophils by plasma from patients with trauma was by a mechanism involving PAF, WEB 2170 (Boehringer-Ingelheim Pharmaceuticals, Ridgefield, Connecticut, USA), a PAF antagonist, was used. Plasma from ten patients with trauma who had an ISS of 25 or more and had plasma samples available for all four time points during the first 24 h was used. Neutrophils from healthy volunteers were pretreated with either WEB 2170 400 μmol/l or buffer for 5 min. Plasma from either a patient or heterologous volunteer at a dilution of 1 · 10 was then added before incubation for a further 5 min. Neutrophils from each of the four tests were pelleted by centrifugation at 1000*g* for 2 min and resuspended in buffer. The neutrophils were then transferred to a microplate and superoxide release measured in response to fMLP 1 μmol/l. Modification of the protocol, i.e. additional centrifugation to separate neutrophils from the priming plasma, resulted in higher recorded amounts of superoxide released than during the original plasma priming experiments.

Plasma interleukin 8

IL-8 levels were determined in the plasma of the first 31 patients enrolled into the study by a commercial sandwich enzyme-linked immunosorbent assay (Bender Medsystems, Vienna, Austria) The primary antibody was a monoclonal mouse immunoglobulin G, and the secondary antibody a horseradish peroxidase-conjugated, polyclonal rabbit antibody. Recombinant 72-amino-acid IL-8 was used to calculate the standard curve.

Statistical analysis

All data are presented as mean(s.e.m.). Demographic data were compared with Student's *t* test or Fisher's exact test. Comparison between control and patients' plasma priming for superoxide release at each time point after injury was with an unpaired *t* test. IL-8 levels at the different time points were compared by analysis of variance. Multivariate regression analyses were performed by treating all variables as continuous and using the computer program SPSS 6.12 (Statistical Package for the Social Sciences, Chicago, Illinois, USA).

Results

Of 52 eligible patients nine were lost because laboratory support staff were not available, and ten because informed consent could not be obtained within 3 h of admission. *Table 1* compares the demographic data, risk factors for MOF and clinical outcomes of enrolled *versus* non-enrolled patients; there were no statistically significant differences apart from increased blood transfusion requirement in the enrolled group. Mean (range) age of enrolled patients was 28 (18–55) years and they were predominantly male. Injuries were equally distributed between blunt (16) and penetrating (17) mechanisms. ISS ranged from 16 to 57, while transfusion requirement in the first 12 h varied from 0 to 49 units of packed red blood cells. There was no correlation between ISS and the amount of blood transfused ($r = 0 \cdot 02$, $P = 0 \cdot 90$). Of the 33 patients studied, seven developed MOF. Patients who developed MOF were more severely injured ($P = 0 \cdot 05$), received a larger blood cell transfusion, and had more septic and non-septic complications, longer admissions to the ICU and a higher mortality rate ($P < 0 \cdot 01$, *Table 2*).

Plasma priming

Incubation time. Plasma sampled from patients with trauma and incubated with neutrophils from normal volunteers for 5 min primed the neutrophils significantly more than plasma sampled from heterologous volunteers (mean(s.e.m.) 1·36(0·10) *versus* 0·56(0·06) nmol superoxide per min per $1 \cdot 3 \times 10^6$ neutrophils, $P < 0 \cdot 01$).

Table 1 Characteristics of all eligible patients with trauma to the torso admitted during the study period

	Enrolled ($n = 33$)	Non-enrolled ($n = 19$)	P
Age (years)*	28 (18–55)	30 (18–55)	0·64¶
Sex ratio (M:F)	28.5	16:3	1·00**
Mechanism of injury (blunt.penetrating)	16·17	7:12	0·56**
ISS*	26 (16–57)	27 (16–50)	0·99¶
Systolic blood pressure (mmHg)*‡	102 (0–156)	107 (0–160)	0·69¶
Red blood cell transfusion (units)*§	16 (0–49)	8 (0–33)	0·04¶
Highest base deficit (mEq/l)*§	14 (8–24)	12 (6–20)	0·08¶
Highest lactate level (mmol/l)*§	4·1 (2·0–7·4)	3·6 (1·2–6·7)	0·33¶
Minor septic complications†	8 (24)	2 (11)	0·29**
Major septic complications†	12 (36)	3 (16)	0·20**
Non-septic complications†	14 (42)	4 (21)	0·14**
ICU stay (days)*	15 (2–93)	7 (1–44)	0·14¶
Multiple organ failure†	7 (21)	1 (5)	0·13¶
Death†	4 (12)	0 (0)	0·28¶

*Values are median (range); †values in parentheses are percentages. ‡In the emergency room; §during the first 12 h. ISS, Injury Severity Score; ICU, intensive care unit. ¶Student's t test; **Fisher's exact test

Incubation of normal neutrophils in patients' plasma for 15 min (mean(s.e.m.) 1·36(0·13) *versus* 0·54(0·07) nmol/min), 30 min (1·20(0·09) *versus* 0·52(0·10) nmol/min) and 60 min (1·21(0·12) *versus* 0·53(0·09) nmol/min) also resulted in significant neutrophil priming ($P < 0·01$).

Time course after injury. Mean(s.e.m.) neutrophil priming by all patients' plasma sampled at 3 h after injury was 1·26(0·19) nmol/min, which was significantly more than that by control plasma ($P < 0·01$). Plasma sampled at 6 h (mean(s.e.m.) 1·33(0·26) nmol/min, $P < 0·01$), 12 h (1·04(0·14) nmol/min, $P < 0·01$) and 24 h (0·86(0·13) nmol/min, $P = 0·02$) after injury also significantly primed normal neutrophils, but plasma sampled after 24 h did not (*Fig. 1*). Neither age, sex, mechanism of injury, ISS, systolic blood pressure in the emergency department, number of units of red blood cells transfused, base deficit nor serum lactate level contributed significantly to the level of plasma priming. The level of plasma priming at 3 h was no different in patients who did or did not develop MOF (mean(s.e.m.) 2·21(0·76) *versus* 1·11(0·17) nmol/min, $P = 0·06$), 6 h (0·91(0·48) *versus* 1·43(0·30) nmol/min, $P = 0·44$), 12 h (1·15(0·34) *versus* 1·00(0·15) nmol/min, $P = 0·69$) or 24 h (1·17(0·25) *versus* 0·75(0·14) nmol/min, $P = 0·16$) after injury.

WEB 2170 inhibition of plasma priming. In this experiment, normal donor neutrophils incubated in heterologous control plasma released mean(s.e.m.) 3·6(0·3) nmol/min. Pretreatment of neutrophils with WEB 2170 before incubation with heterologous donor plasma did not decrease superoxide release (mean(s.e.m.) difference 2·7(6·5) per cent, $P = 0·85$). Priming by patients'

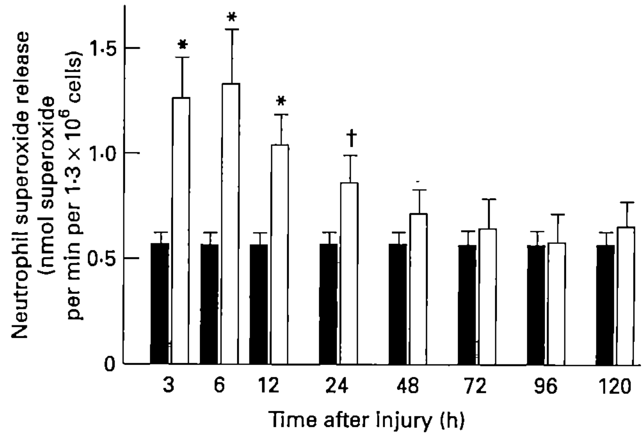

Fig. 1 Time course after injury of normal neutrophil priming by plasma from patients with trauma. Neutrophils from healthy volunteers were incubated for 5 min in either heterologous control plasma (■) or plasma from patients (□) sampled at 3, 6, 12, 24, 48, 72, 96 and 120 h after injury. After incubation, neutrophil superoxide release was measured in response to N-formyl-methyl-leucyl-phenylalanine 1 μmol/l to test for neutrophil priming. Values are mean(s.e.m.). *$P < 0·01$, †$P = 0·02$ *versus* control (unpaired t test)

Table 2 Characteristics of patients who did or did not develop multiple organ failure

	MOF ($n = 7$)	No MOF ($n = 26$)	P
Age (years)*	32 (21–56)	28 (18–46)	0·26¶
Sex (M.F)	6:1	22:4	0·57**
Mechanism of injury (blunt.penetrating)	5.2	11:15	0·43**
ISS*	33 (16–57)	25 (16–41)	0·05¶
Systolic blood pressure (mmHg)*‡	116 (96–146)	98 (0–156)	0·31¶
Red blood cell transfusion (units)*§	26 (3–49)	12 (0–37)	<0·01¶
Highest base deficit (mEq/l)*§	15 (11–19)	13 (8–24)	0·56¶
Highest lactate level (mmol/l)*§	5·4 (3·2–6·6)	3·7 (2·0–7·4)	0·01¶
Minor septic complications†	6 (86)	2 (8)	<0·01**
Major septic complications†	7 (100)	4 (16)	<0·01**
Non-septic complications†	6 (86)	8 (32)	<0·01**
ICU stay (days)*	38 (4–93)	7 (2–32)	<0·01¶
Death†	4 (57)	0 (0)	<0·01**

*Values are median (range); †values in parentheses are percentages. ‡In the emergency room; §during the first 12 h. ISS, Injury Severity Score; ICU, intensive care unit. ¶Student's t test; **Fisher's exact test

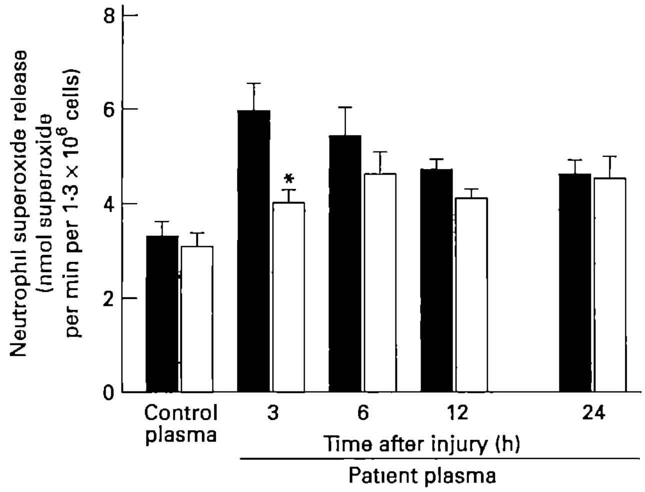

Fig. 2 WEB 2170 (a platelet-activating factor antagonist) inhibition of plasma priming. Neutrophils from healthy volunteers were pretreated with either buffer (■) or WEB 2170 (□) before incubation for 5 min in either heterologous control plasma or plasma from patients sampled at 3, 6, 12 and 24 h after injury. After incubation, neutrophil superoxide release was measured in response to N-formyl-methyl-leucyl-phenylalanine 1 μmol/l to test for neutrophil priming. Values are mean(s.e.m.) $^*P<0{\cdot}01$ (paired t test)

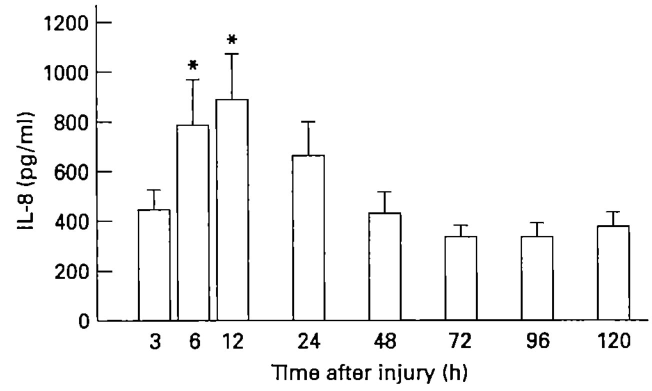

Fig. 3 Plasma interleukin (IL) 8 levels after injury. Values are mean(s.e.m.). $^*P<0{\cdot}05$ *versus* 72 and 96 h (analysis of variance)

plasma sampled at 3 h after trauma was inhibited by 63·8(7·0) per cent by WEB 2170 pretreatment ($P<0{\cdot}01$). WEB 2170 did not significantly inhibit priming by patients' plasma sampled at 6 h (mean(s.e.m.) inhibition 19·8(15·5) per cent), 12 h (30·1(15·7) per cent) and 24 h (9·2(20·1) per cent) after trauma ($P>0{\cdot}05$) (*Fig. 2*).

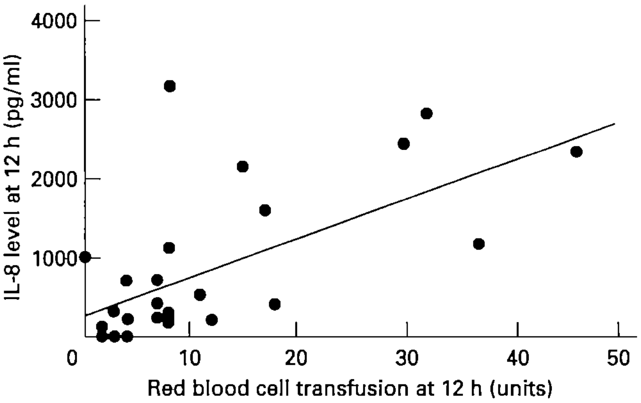

Fig. 4 Correlation between plasma interleukin (IL) 8 level and units of red blood cells transfused at 12 h after major trauma ($r=0{\cdot}64$, $P<0{\cdot}01$)

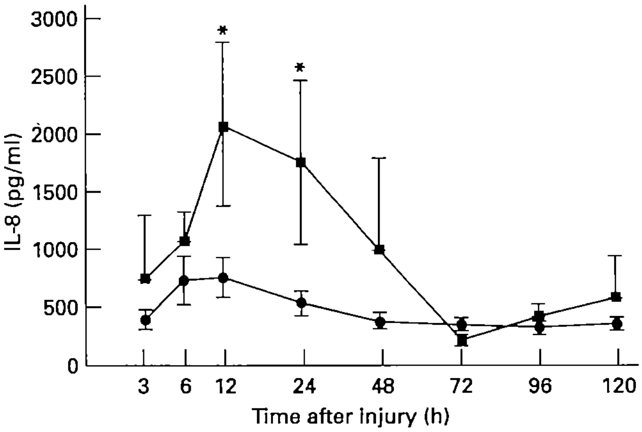

Fig. 5 Plasma interleukin (IL) 8 levels in patients who did (■) and did not (●) develop multiple organ failure (MOF). Values are mean(s.e.m.). $^*P<0{\cdot}05$ (MOF *versus* no MOF, analysis of variance)

Interleukin 8 levels after injury

Mean(s.e.m.) plasma IL-8 levels at 6 and 12 h after trauma were significantly increased to 785(183) and 836(175) pg/ml compared with the levels of 328(47) and 333(54) pg/ml at 72 and 96 h respectively ($P<0{\cdot}05$; *Fig. 3*). When plasma IL-8 levels at 12 h after trauma were correlated univariately with the recorded demographic data and risk factors for MOF, sex ($r=0{\cdot}58$, $P<0{\cdot}01$), lactate level at 12 h ($r=0{\cdot}54$, $P<0{\cdot}01$) and units of red blood cells transfused ($r=0{\cdot}64$, $P<0{\cdot}01$; *Fig. 4*) correlated significantly. However, in a stepwise multivariate analysis, units of red blood cells transfused was the only variable remaining in the equation to predict the plasma IL-8 level ($P<0{\cdot}01$). In the six patients who developed MOF, mean(s.e.m.) plasma IL-8 levels at 12 and 24 h after injury were 2081(715) and 1754(715) pg/ml respectively, and were significantly higher than those of 754(174) and 535(102) pg/ml in patients who did not develop MOF ($P<0{\cdot}05$; *Fig. 5*). In a stepwise multivariate analysis using all variables correlating with MOF ($P<0{\cdot}2$), i.e. ISS, mechanism of injury, lactate level, red blood cell transfusion, neutrophil count and plasma IL-8 level, only plasma IL-8 remained in the equation to predict MOF ($P<0{\cdot}01$).

Discussion

The terms 'ebb phase' (immediately following injury) and 'flow phase' (approximately 24 h to 7 days after injury) have been used to describe the changes in metabolism after injury[6]. The flow phase is the result of increased secretion of 'stress' or counter-regulatory hormones, such as catecholamines, cortisol, glucagon, growth hormone and insulin, resulting in increased gluconeogenesis, catabolism of muscle protein, protein and urinary nitrogen excretion, oxygen consumption and resting energy expenditure[7]. However, these hormones do not account for the ebb phase changes such as the haemodynamic shock response, decrease in level of proteins such as albumin, prealbumin and fibrinogen, or the increase in acute phase proteins such as C-reactive protein, fibrinogen and antiproteases[7]. Nor can the changes be explained by neuronal stimulation alone. Various 'mediator' groups of substances have been added to the historically well established hormones and neurotransmitters. These mediators are defined as communication molecules derived from one cell type that act on another by virtue of specific receptors, and are intermediate in lifespan between the long-lived hormones and the short-lived and locally acting neurotransmitters[7,8]. Their action is limited by effective control or removal processes in the tissues. Mediators, which include PAF, eicosanoids and cytokines, have been proposed as the substances responsible for the ebb or acute phase changes after injury. To prevent or limit acute phase changes and injury to end organs such as the lungs, it is crucial that the exact nature and timing of inflammatory mediator release early after major trauma is elucidated. Of particular importance are mediators with proinflammatory effects on neutrophils since neutrophils have been identified as central effector cells in acute end-organ injury and MOF after trauma. The authors have previously shown priming and activation of circulating neutrophils during the first 24 h after major trauma[4].

Data from this study show that plasma sampled from patients with major torso trauma at 3, 6, 12 and 24 h after injury contained mediators that primed normal neutrophils. The fact that plasma primed normal neutrophils very rapidly (within 5 min) excludes most protein mediators, as well as endotoxin which primes in 30 min, and points towards lipid mediators such as PAF or IL-8 as the plasma priming agents[13,23–25]. Plasma priming at 3 h after injury was inhibited by WEB 2170, indicating that priming was via a mechanism involving PAF, but priming from 6 to 24 h was not inhibited by WEB 2170. Although WEB 2170 is not absolutely specific for PAF, this bioassay provides a strong indication that PAF was present in the plasma at 3 h after trauma, and that from 6 to 24 h different mediators, e.g. complement fragments, IL-6 and IL-8, were responsible for plasma priming. Direct measurement of PAF in the plasma is difficult and labour intensive, but will be required to identify PAF beyond any doubt. Plasma IL-8 levels were increased at 6 and 12 h after injury. Thus, as in models of local inflammation, IL-8 appeared in the circulation some hours after PAF. Interestingly, plasma IL-8 level at 12 h after injury correlated directly with the number of units of red blood cells transfused up to that point. Plasma IL-8 was two and a half times higher in patients who went on to develop MOF, and remained raised until 24 h after injury in these patients. Plasma IL-8 level at 12 h after injury is a better predictor of MOF than ISS, red blood cell transfusion or plasma lactate level. Neutrophil priming by plasma from patients who developed MOF was not different from that in those who did not, which may indicate that priming by IL-8 is a threshold rather than linear phenomenon.

The most likely sources of circulating mediators such as PAF and IL-8 after major trauma are direct mechanical tissue injury, ischaemia–reperfusion of tissue beds and blood transfusion. After mechanical injury, humoral mediators are released to effect a local inflammatory response but also spill over into the systemic circulation[7,26]. Resuscitation of trauma victims after variable periods of haemorrhagic shock may result in ischaemia–reperfusion injury, particularly in the gut which undergoes disproportionate vasoconstriction[27]. During ischaemia, phospholipase A_2 is activated which in turn results in the release of PAF[16]. Reperfusion of ischaemic tissues leads to the generation of free radicals and other reactive oxygen metabolites which are potent proinflammatory stimuli, and results in the release of prostaglandins, leukotrienes, PAF and cytokines, as well as promoting neutrophil–endothelial cell interaction[14,16,27,28]. Major blood transfusion can be associated with acute lung injury as well as delayed immunosuppression and infectious complications after surgery[19,27]. The mechanisms of transfusion-induced end-organ injury as well as immunosuppression remain largely unclear, but the fact that stored autologous and allogeneic blood have similar immunosuppressive effects points to the storage procedure as a significant factor[29]. Of particular importance is the leucocyte count and leucocyte release of cytokines in stored blood products. Nanomolar amounts of cytokines, including IL-8, have been detected in stored platelet concentrates, with lower levels in stored red blood cells[30]. Stored blood components also contain proinflammatory mediators similar to PAF[18]. These proinflammatory mediators can prime circulating neutrophils as well as stimulate endothelial cells, thereby promoting neutrophil sequestration in uninjured end organs, and setting the stage for neutrophil-mediated end-organ injury[31,32].

Clinical studies attempting to eliminate individual mediators responsible for acute inflammation-induced end-organ injury have met with some success. Marzi *et al.*[33] used systemic superoxide dismutase in patients with major trauma to limit free radical damage. PAF receptor antagonists have been used in the clinical settings of acute pancreatitis, sepsis and post-transplant renal failure[34–36]. Also on the horizon are bradykinin receptor antagonists[37]. Anticytokine studies have been less successful. Soluble receptors for tumour necrosis factor (TNF) α have been cloned and administered parenterally in an attempt to neutralize TNF-α and prevent neutrophil activation[38]. Current trials are under way to test anti-IL-6 strategies in sepsis and burns. However, numerous inflammatory cascades and mediators are released after trauma and it is therefore unlikely that use of a single agent would be effective in preventing neutrophil-mediated end-organ injury. Safety in transfusing allogeneic blood products is continuously being improved, and reducing the amount of leucocytes and leucocyte products in packed red cell and platelet concentrates may prove crucial in reducing many of the immunological side-effects of a major blood transfusion[39].

In conclusion, this preliminary study has shown that PAF activity and IL-8 are expressed sequentially in the circulating plasma within hours after major trauma. PAF and IL-8 may be the mediators responsible for priming of neutrophils in these patients at risk of MOF. Plasma IL-8 levels correlated directly with the number of units of red blood cells transfused, and may be an early biological marker of patients who are likely to develop MOF after trauma.

Acknowledgements

The authors thank Professor Michael Hobsley for help with organizing and analysing the data for this manuscript. This work was supported in part by National Institutes of Health grants P50GM49222-0 and T32GMO8315.

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British Journal of Surgery 1996, 83, 1413–1414

Conservative management of infective mastitis and breast abscesses after ultrasonographic assessment

R. J. O'HARA, S. P. L. DEXTER and J. N. FOX

Department of Surgery, Hull Royal Infirmary, Hull, UK
Correspondence to. Mr J. N. Fox, Castle Hill Hospital, Castle Road, Cottingham HU16 5JQ, UK

Current practice in this unit for a suspected breast abscess is preliminary ultrasonographic scan, aspiration of any pus, antibiotic therapy and repeat aspiration in the outpatient clinic if necessary. Inflammatory masses are treated with antibiotics alone. A retrospective review of this strategy has been made. Over a 2-year interval 53 patients were admitted to hospital with a suspected breast abscess. Twenty-two abscesses were aspirated, of which 19 resolved and three required subsequent incision and drainage. Eight patients underwent primary incision and drainage, one of whom required a second drainage procedure. In five patients the abscess discharged spontaneously before intervention. The remaining 18 patients were found on ultrasonography to have inflammation without evidence of focal pus which settled with antibiotic therapy in all but two patients. One of these was found to have an inflammatory cancer and the other developed an abscess, which was drained. Aspiration combined with ultrasonographic imaging is an effective alternative to incision and drainage.

The conventional treatment of a breast abscess is incision and drainage[1]. This usually requires a general anaesthetic, possibly an overnight stay in hospital and regular dressing. In the lactating patient this causes distress to both mother and baby. The incision may also produce an unsatisfactory cosmetic result. In non-lactating abscesses, most of which are related to periductal mastitis, incision and drainage may be associated with recurrence and mammary duct fistula[2].

Aspiration of pus combined with antibiotic therapy is another option[3]. However, breast abscesses may be multilocular and inadequately drained by aspiration[4]. The role of ultrasonographic imaging in the assessment of a suspected breast abscess is established and the technique can be used to assess the adequacy of pus aspiration[5].

Current practice in this unit for a suspected breast abscess is an ultrasonographic scan to demonstrate the presence or absence of pus, aspiration under ultrasonographic guidance or after skin marking, antibiotic therapy and outpatient follow-up for repeated aspiration, if necessary. Inflammatory masses without evidence of pus are treated with antibiotics alone. A retrospective review has been performed of this strategy.

Patients and methods

Records of all patients admitted to the surgical acute admissions ward of the Hull Royal Infirmary between January 1993 and December 1994 with a provisional diagnosis of breast abscess were reviewed Special note was made of the use of diagnostic ultrasonography, the technique and outcome of intervention, and the occurrence of any complications.

The treatment of individual patients during the study was dependent on the admitting surgical team. This accounts for the variability in the use of ultrasonography and of primary aspiration or surgical drainage of pus.

Results

Over the 2 years 53 women were seen with a suspected breast abscess. Details of the patients are shown in *Table 1*. Some 36 women (68 per cent) had an ultrasonographic scan as part of their initial management, while the remainder were treated according to clinical features alone. In seven cases this included 'blind' aspiration.

No focal collection was seen in 19 of the 36 women who had a scan. One of these scans was falsely negative. One woman clinically had an abscess, despite the findings on ultrasonography, and had immediate incision and drainage. There were no false-positive scans. The sensitivity was therefore 95 per cent and the specificity 100 per cent.

In the series of 53 patients, 35 (66 per cent) were found to have an abscess and 18 (34 per cent) had inflammatory change with no focal collection, using ultrasonographic and clinical evidence. Sixteen of the 18 patients with inflammation alone settled with antibiotic treatment and no further intervention. Of the two patients whose symptoms did not resolve, one developed an abscess after 3 days of antibiotics and was considered a treatment failure. This was incised surgically and subsequently healed. The other patient in this group was found to have an inflammatory cancer, which was confirmed by fine-needle cytology. Twenty-two patients underwent aspiration; nineteen abscesses were treated successfully, although one patient developed a persistent sinus which eventually settled without intervention. In two patients delayed surgical drainage was required. One refused repeat aspiration and required incision and drainage of the residual abscess. One further abscess did not settle with aspiration and 200 ml pus were subsequently drained by formal incision.

Of eight patients treated by primary incision and drainage, one required further surgical drainage and one

Table 1 Details of patients admitted with a suspected breast abscess

Total no.	53
Mean (range) age (years)	35 (15–93)
Lactating patients*	17 (32)
Non-lactating patients*	36 (68)
Diabetic patients*	2 (4)

*Values in parentheses are percentages

Paper accepted 18 April 1996

Table 2 Isolation of bacteria from breast abscesses

Bacterial growth	Lactational abscess	Non-lactational abscess
Staphylococcus aureus	9	6
S. aureus and diphtheroids	—	1
S. epidermidis	—	3
Bacteroides spp.	—	3
Bacteroides spp. and peptostreptococcus	—	2
Bacteroides spp. and *Proteus mirabilis*	—	1
P. mirabilis	—	4
No growth	—	3

has been left with a scarred deformity of the nipple. In five women the abscess drained spontaneously; four resolved without complication, but one patient developed a mammary duct fistula. Four of the five were treated with antibiotics.

Whereas pus from lactational abscesses grew exclusively *Staphylococcus aureus*, a variety of organisms were isolated from non-lactational abscesses (*Table 2*).

Nine of 17 lactational infections were initially considered inflammatory on ultrasonography. Eight of these responded to antibiotics alone, but one patient returned after 3 days with an abscess.

Discussion

This retrospective review of 53 patients with the clinical features of a breast abscess demonstrated that 18 patients (34 per cent) did not have a collection of pus. An ultrasonographic scan therefore could prevent about one-third of patients undergoing unnecessary surgical intervention.

Management based on ultrasonographic findings led to failure of conservative treatment in only four of 36 patients. In one of these the scan was falsely negative and the abscess was drained. In a second, antibiotics failed to resolve the lesion and an abscess developed after 3 days. In the other two shown to have a collection of pus, aspiration of a very large abscess was probably inadequate in one patient, and the second patient declined further aspiration on the grounds of discomfort of the procedure. Whilst some patients experience discomfort during the procedure, prior application of local anaesthetic (EMLA) cream reduces pain and makes aspiration acceptable.

Blind aspiration without ultrasonographic imaging was done in seven patients, usually when the abscess was superficial and easy to localize. In one case this failed, underlining the usefulness of ultrasonographically-guided aspiration.

The finding of an inflammatory cancer emphasizes the need for follow-up imaging and, if necessary, fine-needle cytology on patients with inflammatory breast conditions before discharge from the clinic.

Thirty-six breast infections (68 per cent) were non-lactational. The range of bacteria isolated from the abscesses confirms the need to use broad-spectrum antibiotics active against anaerobic activity, rather than the traditional antistaphylococcal antibiotic therapy[6].

Although incision and drainage has been regarded as appropriate treatment for breast abscess, aspiration is an effective alternative. Assessment by ultrasonography confirms the need for intervention and facilitates aspiration. The combined use of ultrasonographic imaging and aspiration should enable almost all inflammatory breast conditions to be managed conservatively in the breast clinic.

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British Journal of Surgery 1996, 83, 1415–1416

Image-guided core biopsy in patients with breast disease

M. J. B. CHARE, C. I. FLOWERS*, C. J. O'BRIEN† and A. DAWSON†

*Departments of Surgery, *Radiology and †Pathology, Neath General Hospital, Neath and Breast Test Wales, Swansea, UK*
Correspondence to: Mr M. J. B. Chare, Neath General Hospital, Neath SA11 2LQ, UK

Ultrasonographically-guided core biopsy has been used as an adjunct to triple assessment when fine-needle aspiration cytology was inadequate or equivocal, if the overall assessment of the patient was uncertain, or if it was deemed the preferred diagnostic option. Some 143 of 2603 patients had a guided core biopsy, 125 to establish the diagnosis and 18 to obtain histology in cytologically proven malignancy. A diagnosis of malignancy was established in 43 of the 125 patients who had a diagnostic core biopsy. Some 45 patients with benign disease were either discharged or returned to follow-up on the basis of the core biopsy. The remaining 37 patients required surgical biopsy, of whom 13 had malignant and 24 benign disease. The overall positive predictive value for malignancy was 98 per cent. Experience with ultrasonographically-guided core biopsy shows that it can reduce the need for surgical biopsy in both benign and malignant conditions of the breast.

Triple assessment by clinical examination, mammography and fine-needle aspiration cytology (FNAC) is now established in the appraisal of patients with breast disease[1]. If the findings of the triple assessment accord, firm management recommendations may be made, otherwise surgical biopsy is usually required to establish the diagnosis. Image-guided core biopsy using stereotactic[2,3] or ultrasonographic[4] guidance is now used increasingly as an adjunct to triple assessment and may reduce the need for surgical biopsy.

Core biopsy with stereotactic guidance has been used mainly in the diagnosis of impalpable lesions, but needs expensive equipment and special expertise. Ultrasonographically-guided core biopsy, however, may be used in any specialist breast clinic using current ultrasonography equipment, without the need for major investment. This technique was used in the authors' breast clinics since August 1994, and experience gained to date is reported.

Patients and methods

The 2603 patients studied were seen by the breast team between 1 August 1994 and 31 January 1996. Some 2298 of these patients were referred to Neath Breast Clinic and the remaining 305 were seen in the Assessment Clinic at Breast Test Wales in Swansea. Both of these clinics are 'one-stop' clinics where the results of both breast imaging and clinical or image-guided FNAC are available during the clinic. A total of 125 of the 2603 patients underwent diagnostic ultrasonographically-guided core biopsy during the initial clinic visit. This was indicated if the cytology was inadequate C1 (30 patients) or equivocal C3 or C4 (41 patients), if the overall assessment of the patient was uncertain (20 patients), or if it was deemed the preferred diagnostic option (34 patients). In 18 patients it was used to obtain a histological diagnosis in a cytologically proven malignancy.

All procedures were performed under local anaesthetic with a 16-G needle with a 2·2-cm throw, using an automated core biopsy gun (Manan Promag 2·2; Kimal, Uxbridge, UK). Real time ultrasonographic visualization of the needle in the lesion at the time of the biopsy resulted in increased accuracy of sampling, even in clinically palpable lesions Care was taken to make sure the needle travelled parallel to the chest wall to avoid the possibility of pneumothorax, and at least three passes were made. Patients were seen in the clinic the following week with their results.

Image-guided core biopsy was considered the preferred alternative to cytology in 34 patients. Most commonly this was because the clinico-radiological findings were vague or diffuse suggesting lobular carcinoma or ductal carcinoma *in situ* (DCIS) (11 patients), if there was suspected recurrence in a conserved breast after radiotherapy (six) or if the patient was being considered for primary medical treatment (four). The procedure was used for patients re-referred to the clinic with the same clinical problem (seven patients) and also where there was a mass suggestive of a lipoma or fat necrosis (five), as in these conditions FNAC may show cells which are consistent with, but not diagnostic of, the pathology. In one patient the procedure was undertaken because bloodstained fluid was obtained during the aspiration of a complex cyst.

Results

Ultrasonographically-guided biopsy was well tolerated, although the degree of bruising noted by most patients was greater than that seen after FNAC. There were no significant side-effects following image-guided core biopsy.

The outcome of the 125 diagnostic core biopsies is summarized in *Table 1*. In 88 of the 125 patients undergoing diagnostic ultrasonographically-guided core biopsy a definite decision could be made regarding management; 43 patients had a diagnosis of malignancy and proceeded to primary treatment, and 45 patients with benign disease were discharged or returned to follow-up. A further ten patients elected to have the lesion excised despite benign assessment and benign core biopsy. The remaining 27 patients required surgical biopsy, of which 13 had malignant and 14 benign lesions.

Combining biopsies that were suspicious with those that were diagnosed as malignant resulted in a sensitivity of 80 per cent and specificity of 99 per cent. The positive predictive value for malignancy was 98 per cent, with a prevalence of 45 per cent. There were no 'true' false positives but one patient with a suspicious core biopsy had a benign papilloma and atypical hyperplasia. These figures for core biopsy are set against a high-quality FNAC service which has an absolute sensitivity for the same population of patients of 70 per cent.

Eighteen patients with a diagnosis of malignancy established by triple assessment also underwent ultrasonographically-guided core biopsy. In ten this was performed to assess the tumour type and grade before medical treatment, to exclude DCIS, which cannot be differentiated from invasive disease by cytology alone, and

Paper accepted 20 June 1996

Table 1 Outcome in 125 patients undergoing diagnostic core biopsy

Core biopsy histology	Clinical or radiological assessment	No.	Outcome	Final diagnosis after surgical biopsy
Malignant	Suspicious or malignant	43	Primary treatment	
Benign	Benign	45	Discharged/followed up	
Benign	Benign	10	Excision of lesion*	Benign 10
Suspicious of malignancy	Suspicious or malignant	3	Open biopsy	Benign 1† Malignant 2
Normal or benign	Uncertain or suspicious	24	Open biopsy	Benign 13 Malignant 11

*Lesions were excised at the patient's request despite an overall benign assessment; †histology was benign papilloma with associated atypical hyperplasia

to establish oestrogen receptor status in patients treated with tamoxifen alone. In two of the ten patients metastatic disease from a primary in the colon or lung was found. In the remaining eight patients with vague radiological findings or diffuse microcalcification, core biopsy confirmed either lobular carcinoma (four patients) or DCIS (four).

Discussion

Ultrasonographically-guided core biopsy is a safe technique that allows both palpable and impalpable lesions to be biopsied accurately during the patient's initial visit to the breast clinic. This accuracy makes the technique preferable to repeat FNAC when the result is inadequate or equivocal. This is achieved at little extra cost over that of FNAC, yet has the potential of greater than tenfold saving on the costs of a surgical biopsy.

Although ultrasonographically-guided core biopsy is of value only in patients whose radiological lesion is visible on ultrasonography, these results are comparable to those obtained using the prone table stereotactic digital imaging system for core biopsy[5]. Nevertheless, as lesions such as microcalcification, which are visible on mammography only, cannot generally be biopsied using this technique, the full potential of image-guided core biopsy can only be realized by the availability of both ultrasonography and stereotactic guidance in a breast clinic.

Experience with ultrasonographically-guided core biopsy shows that it is an inexpensive technique which can reduce the need for surgical biopsy for both benign and malignant conditions of the breast.

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British Journal of Surgery 1996, 83, 1417–1418

Use of covered expandable metal stents in the treatment of oesophageal carcinoma and tracheo-oesophageal fistula

T. A. COOK and T. C. B. DEHN

Department of Surgery, Royal Berkshire Hospital, London Road, Reading RG1 5AN, UK
Correspondence to: Mr T. C. B. Dehn

Palliation for malignant dysphagia has relied on oesophageal dilatation, insertion of rigid prostheses and laser treatment. All three methods have substantial risk of perforation. Displacement of the tube is also well described. Seventeen expandable polyethylene-covered metal stents were inserted in 15 patients with oesophageal carcinoma; there were 11 men and four women, of median age 70 years. Thirteen stents were inserted for dysphagia and four for tracheo-oesophageal fistula (TOF). Stents were inserted endoscopically under fluorosopic control. Seven patients died from their disease a median of 5 (range 1–11) months after stent insertion. Median follow-up in the remainder is 6 (range 1–11) months. Median dysphagia scores before and after insertion were 3 (range 2–4) and 1 (range 1–2) respectively. Stent insertion provided cure of symptoms in patients with TOF. Median hospital stay following insertion was 2 (range 1–20) nights. There were no deaths and no perforations associated with the procedure. Two patients complained of retrosternal chest pain for 2 days after stent insertion. One patient presented with dysphagia related to later stent migration. There has been no deterioration in symptoms of dysphagia in the remainder. Expandable oesophageal stents offer a safe alternative to traditional methods of palliative treatment for oesophageal carcinoma. In the long term they may provide a cost-effective alternative to standard treatments.

Palliation of dysphagia may be the only treatment attainable in up to 60 per cent of patients with oesophageal carcinoma[1]. The life expectancy of patients with irresectable oesophageal tumours is measured in months. Successful palliation should achieve effective relief of dysphagia with both minimal risk and short hospital stay. The purpose of this study was to assess the effectiveness of covered expandable metal stents in achieving these goals and to determine the length of hospitalization in patients undergoing stent placement.

Patients and methods

Seventeen expandable polyethylene-covered metal stents (Cook, Letchworth, UK) were inserted in 15 patients with oesophageal carcinoma; there were 11 men and four women of median age 70 (range 52–89) years. There were two middle-third tumours, 12 lower-third lesions and one at an anastomosis in a patient who had undergone oesophagogastrectomy 17 months previously. There were two squamous cell carcinomas and the remainder were adenocarcinomas. Median tumour length was 5 (range 3–10) cm. Thirteen stents were inserted for dysphagia and four for tracheo-oesophageal fistula (TOF) Stents were inserted endoscopically, without prior dilatation, under fluoroscopic control. Assessment of swallowing was made by direct questioning on admission, at discharge and at 6-weekly follow-up using dysphagia scores (0, normal swallowing; 1, dysphagia to some solids, 2, tolerates semisolid diet only; 3, tolerates liquids only; 4, aphagia). Patients were followed until death

Results

Seven patients died from their disease a median of 5 (range 1–11) months after stent insertion. Median follow-up in the remainder is 6 (range 1–11) months. Median dysphagia scores before and after insertion were 3 (range 2–4) and 1 (range 1–2) respectively (*Fig. 1*). Stent insertion provided immediate cure of symptoms in the three patients with malignant TOF on four occasions (one man developed a second and more proximal TOF requiring a further stent). Median hospital stay following insertion was 2 (range 1–20) nights.

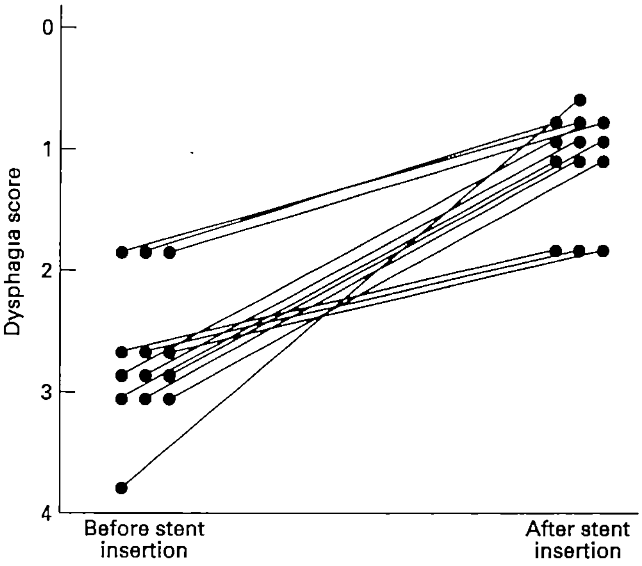

Fig. 1 Dysphagia scores before and after stent insertion

There were no deaths and no perforations associated with the stent insertion. Two patients complained of retrosternal chest pain for 2 days following the procedure but there were no other complications associated with insertion. One patient developed a TOF following radiotherapy for recurrent oesophageal tumour 4 months after stent insertion for relief of dysphagia. A second stent was inserted with successful control of TOF symptoms. This man developed a second and more proximal TOF and a third stent was successfully inserted. One patient suffered recurrent dysphagia: the stent had migrated

Paper accepted 30 May 1996

Table 1 Breakdown of cost per patient of expandable stent insertion

	£
Endoscopy	150
Two nights in hospital	400
Use of radiography department per hour	50
Stent	600
Total cost per patient	1200

distally into the stomach. This patient subsequently underwent laser therapy. There has been no deterioration in symptoms of dysphagia in the remainding patients. *Table 1* shows a breakdown of the cost of stent insertion. Median time for stent insertion (from patients entering to leaving the fluoroscopy room) was 48 (range 36–81) min.

During the period of study six other patients with oesophageal cancer, aged 55 (range 21–75) years, deemed irresectable on the grounds of comorbidity or metastatic disease, were palliated by other means: laser for bleeding tumours (three patients), chemotherapy (two) and radiotherapy (one).

Discussion

Palliation of oesophageal carcinoma has relied on radiotherapy (external beam or intracavitary) and endoscopic procedures (simple dilatation, alcohol injection, laser therapy and intraluminal oesophageal stenting). Laser treatment is effective but may require repeated hospital admissions[2,3]. It may be particularly suitable for treatment of short tumours[4]. Radiotherapy, while effective for squamous cell carcinoma, is less effective in palliating adenocarcinoma and relief of dysphagia may not occur for several weeks[5]. Rigid prostheses provide early symptomatic relief but are associated with a high rate of complications such as perforation and bolus obstruction and a procedure-related mortality rate of up to 6 per cent[6]. One-third of patients require further admission following radiotherapy or insertion of rigid prostheses[7].

Early results using uncovered expandable metal stents were encouraging but tumour ingrowth and recurrent dysphagia were reported[8,9]. These problems have been overcome by using a covered stent. In this series no patient presented with recurrent dysphagia due to tumour growth through or at the ends of the stent. It was found that improvement in dysphagia score was immediate and maintained over the follow-up period. There were no complications associated with insertion. Minimal dilatation (if any) of the tumour is necessary before inserting the 9-mm sheath through which the stent is introduced. Subsequent bolus obstruction is rare because the internal diameter of the stent is 16 mm compared with 12 mm in most rigid prostheses.

Despite the presence of a barb on the stent to aid fixation, distal stent migration occurred in one patient. This may be overcome by immediate balloon dilatation of the stent. It is advisable not to insert expandable stents across soft tumours or those through which the endoscope will pass readily because stent migration is more likely to occur in these patients. The retrosternal chest pain experienced by two patients was due to continuing expansion of the stent over 48 h after insertion. In both cases the pain was controlled with simple analgesics.

Use of rigid stents in the management of TOF has not been encouraging[10]. Early reports have suggested a role for expandable stents in the management of malignant TOF[11]. The authors' experience has shown that expandable stents provide rapid relief of symptoms of malignant TOF. Although inpatient stay was slightly longer than that for patients with dysphagia (3 *versus* 2 nights) it compared favourably with length of stay following conservative treatment.

This observational study has shown four major benefits of expandable stents. First, hospital stay is short (2 nights in the majority of patients although social circumstances required a 20-night stay in one patient). This is shorter than overall hospital stay following rigid stent insertion (9 days)[8] or laser treatment (14 days)[3], or that in other series using expandable stents (4 days)[8,9]. Second, this method does not involve repeated trips to hospital which are required with radiotherapy or laser treatment. Third, there were no readmissions for bolus obstruction or tumour overgrowth. Finally, there was no procedure-related morbidity or death. Treatment of complications and repeated visits to hospital in an elderly group of patients have important cost implications. It is the authors' belief that the initial high cost of expandable stents is amply compensated by the short hospital stay and low procedure-related morbidity. The authors no longer use rigid stents in patients selected for palliation by stenting. Expandable stents may provide a more cost-effective means of palliation of oesophageal carcinoma than rigid stents, laser treatment or radiotherapy.

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British Journal of Surgery 1996, 83, 1419–1420

Port-site metastases in patients undergoing laparoscopy for gastrointestinal malignancy

T. A. COOK and T. C. B. DEHN

Department of Surgery, Royal Berkshire Hospital, London Road, Reading RG1 5AN, UK
Correspondence to Mr T. C. B. Dehn

Laparoscopic colonic resection and laparoscopy for the assessment of malignant disease have been advocated. Metastatic deposits at port sites are recognized but the incidence of these is poorly defined. Forty-six patients, of median age 65 (range 19–90) years, with gastrointestinal malignancy underwent laparoscopy. Eighteen patients died a median of 4 (range 1–28) months after laparoscopy, four following colonic resection and 14 with gastro-oesophageal malignancy; ten had undergone resection. Median follow-up of the 28 survivors is 8 (range 2–39) months. Five of the 46 patients developed port-site recurrence giving an early incidence of port-site recurrence in this cohort of patients of 11 per cent. Five of 20 patients with tumour involving serosal surfaces developed port-site recurrence compared with none of 26 without serosal involvement ($P = 0.022$, Fisher's exact test). Port-site recurrence may be related to serosal involvement with tumour.

Abdominal wound metastases following laparotomy are rare[1]. While laparoscopic resection for colonic carcinoma remains controversial[2], laparoscopy for assessment and staging of upper gastrointestinal malignancies has gained wider acceptance[3–5]. Isolated case reports describe metastatic deposits at port sites and suggest that this occurs more commonly than following laparotomy[6]. Despite increasing awareness of port-site recurrence[6,7], the incidence is poorly defined. The purpose of this study was to determine the early incidence of port-site metastases and attempt to define factors relating to the tumour that might influence their occurrence.

Patients and methods

Between January 1992 and December 1995 laparoscopy was undertaken on 46 patients with gastrointestinal malignancy (median age 65 (range 19–90) years; 38 men, eight women). Patient data were collected prospectively. Five patients underwent laparoscopically-assisted colonic resection, four with known liver metastases, for control of local disease. Another had a single-port laparoscopy for small bowel obstruction immediately before laparotomy for an obstructing caecal carcinoma. The remainder, none of whom had a contraindication to resection on the basis of ultrasonography or computed tomography (CT) assessment, underwent laparoscopy for staging of gastric (ten patients) or oesophageal (30) carcinoma. Five-port laparoscopy was performed in these patients to allow inspection of the lesser sac and appropriate biopsy if indicated. Assessment was made of the presence of liver metastases, ascites, omental or peritoneal deposits and lymph node involvement. Twenty-eight patients subsequently underwent tumour resection. Patients were followed up until death.

Results

Eighteen patients died a median of 4 (range 1–28) months after laparoscopy. Four had had a colonic resection; all had advanced disease at the time of surgery. Eight patients with oesophageal malignancy died, seven of whom had undergone resection. Three of these patients died within 30 days, one from haemorrhage secondary to disseminated intravascular coagulation, one from sepsis resulting in multiorgan failure and one from anastomotic leakage. Six patients with gastric tumours died. Three had undergone resection; two of these patients died within 30 days, one from cardiac tamponade and one from complications of a tunnelled feeding jejunostomy tube. Median follow-up of the 28 survivors is 8 (range 2–39) months. Five of the 46 patients developed port-site recurrence.

Patients 1 and 2

A 71-year-old woman and 61-year-old man with gastric carcinomas were noted at laparoscopy to have a small volume of ascites and omental deposits undetected on preoperative imaging. Both underwent chemotherapy. Umbilical port-site recurrences developed 7 and 1 month later respectively. Both died 2 months later.

Patient 3

At laparoscopy a 19-year-old woman with a lower-third oesophageal adenocarcinoma was found to have liver secondaries, ascites and nodal secondaries. She underwent chemotherapy and initially had a good clinical, radiological and endoscopic response. She developed a port-site recurrence in the left upper quadrant after 10 months and is currently being treated with further chemotherapy.

Patient 4

A 59-year-old woman with known liver metastases underwent a laparoscopically-assisted anterior resection for an obstructing Dukes C carcinoma of the rectosigmoid. She had postoperative chemotherapy and developed a port-site recurrence at the umbilicus 9 months after surgery. She died 1 month later.

Patient 5

A 58-year-old man who had undergone a complicated appendicectomy as a child, presented with small bowel obstruction. A provisional diagnosis of adhesion obstruction was made and laparoscopy was performed via

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Paper accepted 2 June 1996

a single port in the left upper quadrant; an obstructing caecal carcinoma was identified. At this stage, and before tumour manipulation, the operation was converted to an open right hemicolectomy. A Dukes B carcinoma with serosal tumour involvement was confirmed histologically. Fifteen months later the man presented with recurrent subacute bowel obstruction. At subsequent laparotomy a local recurrence was resected. A solitary nodule at the port site was also resected and shown to be metastatic tumour. The laparotomy wound was spared and there was no other peritoneal involvement of tumour.

Serosal involvement of tumour (primary tumour, omental or peritoneal deposits) was present in all five patients. Five of 20 patients with tumour involving serosal surfaces developed port-site recurrence compared with none of 26 without serosal involvement ($P = 0{\cdot}022$, Fisher's exact test).

Discussion

The incidence of port-site recurrence in this cohort of patients was 11 per cent. This is higher than that reported following laparotomy[1] or laparoscopy for gynaecological malignancy[8].

Laparoscopy is more accurate than CT or ultrasonography in detecting liver secondaries and omental or peritoneal tumour deposits[9]. While CT and ultrasonography may detect the presence of enlarged lymph nodes, five-port laparoscopy allows assessment of the degree of fixation and biopsies to be taken. None of the patients in this series had contraindications to laparoscopy on the basis of CT or ultrasonography.

Three factors that relate specifically to laparoscopic surgery may be important in the development of port site recurrence[6]. First, the repeated passage of instruments through the port may bring exfoliated cells adherent to the instrument into close proximity with the port site. Second, increased manipulation of the tumour, which is inevitable with the loss of tactile feedback using laparoscopic instruments, may lead to increased exfoliation of tumour cells. Finally, there are the effects of pneumoperitoneum. Clumps of whole cells have recently been collected in smoke produced by electrocoagulation at laparoscopy[10]. As gas escapes under pressure around port sites these clumps of tumour cells may be seeded into the wound.

Of the five patients with port-site recurrence, four had advanced disease at the time of laparoscopy but the fifth patient had a potentially curable caecal carcinoma. In this latter patient no manipulation of the tumour had been made at initial laparoscopy. The data suggest that port-site metastases may be related to serosal involvement of tumour. Port-site recurrences following resection of Dukes A tumours have been reported[11,12]. However, in one of these studies[11] a colotomy was performed, immediately exposing tumour cells to the peritoneal cavity. In another[12] the recurrence occurred at the site of specimen retrieval with possible trauma to the specimen at the time of extraction[12].

The presence of port-site recurrence may have little bearing on the final outcome of patients with advanced disease. While often painful, their development may be an acceptable price to pay for accurate staging and avoidance of a laparotomy.

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British Journal of Surgery 1996, 83, 1421–1423

Radical lymphadenectomy in the management of early gastric cancer

N. HAYES, D. KARAT, D. J. SCOTT*, S. A. RAIMES and S. M. GRIFFIN

*Oesophago-Gastric Cancer Unit and *Institute of Pathology, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, UK*
Correspondence to: Mr S. M. Griffin

Lymph node metastasis in patients with early gastric cancer was evaluated prospectively to determine whether radical (D_2) lymphadenectomy is appropriate in such cases. Twenty-eight (18 per cent) of 156 patients having surgery for gastric cancer had early disease. Lymph node metastasis was found in 12 of the 28 patients. Metastasis was more likely in submucosal than mucosal early gastric cancer (nine of 14 *versus* three of 14; $P = 0{\cdot}024$, Fisher's exact test). In two of three patients with metastasis at the N_2 level, the N_1 nodes were entirely clear. This study shows a higher incidence of lymph node metastasis than has been reported previously in both the UK and Japan. The high incidence of lymph node metastasis in early gastric cancer supports the continuing use of radical lymphadenectomy in patients who are fit for such major surgery.

Traditionally, patients in the UK with gastric cancer have been perceived to have a poor prognosis. Survival in an individual case is best predicted by the clinicopathological stage of the tumour, and in recent years there has been an increase in the proportion of patients presenting with earlier stage disease[1,2]. It has now been shown that such patients can be treated with the expectation of survival rates to equal the exceptional results hitherto obtained only in Japanese centres[3]. In 1962 the Japanese Endoscopic Society defined early gastric cancer as that in which the depth of tumour invasion is limited to the submucosal layer at worst[4]. This diagnosis has become synonymous with cancer that is amenable to surgical cure, but the debate on what constitutes the optimum surgical management for early gastric cancer has not been concluded.

Some authors have suggested that early gastric cancer can be treated adequately by less aggressive surgery[5] and, furthermore, some Japanese units advocate local endoscopic surgery alone for selected patients with mucosal early gastric cancer[6,7]. Other authorities advocate radical gastrectomy with *en bloc* lymphadenectomy for all patients with gastric cancer in whom cure is a possibility[1,8,9]. The purpose of this study was prospectively to record the lymph node status of patients with early gastric cancer to determine whether an aggressive surgical approach to gastric cancer as a whole is justifiably applied to earlier stage disease.

Patients and methods

This study took place over a period of 48 months from April 1990, and all consecutive patients undergoing surgical exploration for biopsy-proven adenocarcinoma of the stomach were included. Before operation patients were investigated for metastatic disease by abdominal ultrasonography and spiral computed tomography. At laparotomy the surgeon evaluated the disease stage according to guidelines from the Japanese Research Society for Stomach Cancer[10]. It was the policy of this unit for patients to undergo gastrectomy with radical (D_2) lymphadenectomy; however, patients unfit for such major surgery because of coincidental medical conditions underwent a standard resection (D_1). Patients with disseminated peritoneal or hepatic metastases (M_1) underwent palliative surgery only.

Gastrectomy specimens were immediately transferred to the pathology department where the lymph-bearing adnexae were dissected from the stomach and fixed separately in groups or node 'stations' recorded according to Japanese guidelines[10] The stomach was opened while fresh along the greater curvature and pinned to a cork board before fixation. Tumour morphology was recorded with the Borrmann classification for advanced cancers[11] and Murakami's method for early gastric cancer[4]. Lymph nodes were individually dissected from the surrounding fatty tissue after fixation in formaldehyde solution, and histological assessment of each gland was performed in three sections if the 'equatorial' section was negative. The depth of invasion of the primary cancer was examined meticulously, and tumours involving the mucosal or submucosal planes only, irrespective of lymph node status, were categorized as early gastric cancer.

Postoperative complications and deaths were recorded for the period covering 30 days after surgery, or for the hospital stay if it exceeded 30 days.

Results

During the study period 156 patients underwent surgical evaluation with a view to gastrectomy. Twenty-eight patients (18 per cent) (19 men and nine women aged 54–82 years) had early gastric cancer and are discussed further below.

Fifteen patients had a D_1 gastrectomy and the remainder had a D_2 resection. The median (range) number of lymph nodes recovered was 16 (6–25) for D_1 and 20 (10–53) for D_2. Two patients with D_1 resections had a completion gastrectomy for stump cancer after previous surgery for peptic ulcer. *Table 1* shows how the operations were stratified.

Nine patients had positive nodes retrieved from the N_1 tier, one had positive nodes at N_1 and N_2 sites, and two had positive lymph nodes at the N_2 level only. Two patients with early gastric cancer had protruding (type I) tumours; both were node negative. Twenty patients had superficial cancer (type II) and six had excavated or combined cancers (types III or II–III) but the early gastric cancer morphology had no bearing on node status.

Table 1 Lymphadenectomies performed stratified by operation

	D_1	D_2	Total
Total gastrectomy	5	7	12
Subtotal gastrectomy	8	6	14
Completion gastrectomy	2	0	2
Total	15	13	28

Paper accepted 4 July 1996

Table 2 Node status in early gastric cancer according to depth of tumour

Depth of invasion	N_0	N_1	N_2	Total
Mucosa	11	2	1	14
Submucosa*	5	7	2	14
Total	16	9	3	28

*Submucosal cancer had a significantly higher proportion of node-positive cases ($P = 0{\cdot}024$, Fisher's exact test)

However, metastasis to lymph nodes was significantly more likely if the primary tumour had penetrated into the submucosal layer (nine of 14 patients *versus* three of 14 with mucosal cancer; $P = 0{\cdot}024$, Fisher's exact test). *Table 2* shows the nodal status according to depth of tumour.

The 28 operations were performed with no deaths, but complications occurred in two patients. A 58-year-old man had undergone D_2 total gastrectomy and required emergency laparotomy on the 11th postoperative day for secondary haemorrhage from the right gastric artery stump. The second complication was in a 55-year-old man who had a D_2 total gastrectomy and developed a duodenal stump leak on the seventh postoperative day, which closed spontaneously after conservative management. Only limited follow-up data are available for the patients to date, but there have been no deaths from recurrent adenocarcinoma.

Discussion

In this series 12 of 28 patients with early gastric cancer had lymph node metastasis. This includes nine of 14 patients with submucosal cancer, and three of 14 with cancer confined to the mucosal layer. These results contrast sharply with those from either Japan or the West, where lymph node metastases have been found in up to 20 per cent of patients with submucosal cancer and in up to 5 per cent of those with mucosal cancer[3,6,8,12].

There are some factors that suggest that this already high incidence of lymph node metastasis in early gastric carcinoma may be an underestimate. In two of the three cases where nodes in the second tier (N_2) were found to be positive, the first tier nodes were all negative, demonstrating that node 'skipping' can occur. Fifteen of the present patients were considered fit enough for only D_1 lymphadenectomy, and as the N_2 nodes were not sampled in this group there is a potential for understaging. In this study the number of lymph nodes retrieved appears to be lower than that quoted for similar operations in Japanese reports[13,14]. The lymph node retrieval method used involves the dissection of fatty tissue at the node stations after fixation. It is possible that by immediate bench dissection of the fresh specimen, as practised in many Japanese operating departments (T. Sano, personal communication), or by chemical lipid clearance, as described by Wagner and colleagues[15] in Marburg, a greater number of nodes might have been obtained. The limitations of lymph node retrieval make the present findings all the more remarkable.

To explain the difference between the present results and those usually found in the literature, it may be suggested that the primary lesion was understaged. However, the majority of early gastric cancers were less than 4 cm in diameter, and the pathology service routinely takes 5-mm blocks from the entire cancer. Sections are examined from each block, leading to a thorough survey of the vital submucosal–muscularis propria interface across the whole tumour[16]. Hence, the depth of tumour penetration was assessed as meticulously in these specimens as in those from reports published elsewhere.

Second, the Japanese rules on lymph node examination appear to be open to some interpretation; there seems to be a variety of recommended methods of nodal examination, from serial sectioning of all nodes to representative examination of one node per group or station[10]. A meticulous three-section examination of every resected node was chosen for the present study, which probably increased the detection of so-called 'micrometastases'. Such tiny tumour emboli are found in the peripheral sinusoids of the nodes and can be easily overlooked. Gunvén and colleagues[17] have shown that such micrometastases do not necessarily worsen prognosis, as they result in disease upstaging. Far from supporting a reduction in lymph node surveillance, this work encourages attention to detail in order to understand the metastatic process further.

The results of this study suggest that the conservative methods of treatment for early gastric cancer developed by the Japanese[6] are not appropriate in the UK. If a nihilistic approach toward the treatment of early gastric cancer is taken, as has been advocated in the West[5,18], the chance of cure would be denied to a significant proportion of patients. On the basis of this study it is suggested that the role of extended lymphadenectomy in early gastric cancer is proven. Preoperative and operative disease staging is still an inexact science, and the depth of tumour penetration or lymph node status in individual cases cannot yet be decided with certainty before histological confirmation. Preoperative staging of gastric cancer with the use of endoluminal ultrasound probes is being evaluated currently[19], and may eventually be routine. However, at present, the surgeon cannot with any certainty know the stage of a gastric cancer at operation. Radical gastrectomy with extended lymphadenectomy can be performed with an acceptable morbidity and low mortality rate in fit patients and is the treatment of choice in early gastric cancer. Far from suggesting a less aggressive approach for this disease, it is precisely these patients, in whom surgical cure is a realistic goal, who deserve the most radical procedures.

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British Journal of Surgery 1996, 83, 1424–1428

Accuracy of laparoscopic ultrasonography in the staging of upper gastrointestinal malignancy

D. N. ANDERSON, S. CAMPBELL* and K. G. M. PARK

*Departments of Surgery and *Radiology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB9 2ZB, UK*
Correspondence to. Mr K. G M. Park

Laparoscopic ultrasonographic staging was compared prospectively with conventional computed tomography (CT) and ultrasonographic staging of 24 lower-third oesophageal tumours and 20 gastric malignancies. Following laparoscopic ultrasonography, seven patients regarded as being resectable after conventional imaging were excluded from surgical exploration because of ascites with peritoneal deposits (four patients), liver metastases (one), advanced local disease (one) and poor tolerance of general anaesthesia (one). Preoperative T and N stages were compared with the pathological staging following resection in 34 patients. Laparoscopic ultrasonography was significantly more accurate than conventional CT and ultrasonography in assessment of the primary tumour (91 *versus* 64 per cent, $P<0{\cdot}01$) and nodal status (91 *versus* 62 per cent, $P<0{\cdot}05$). The addition of laparoscopic ultrasonography to conventional procedures for staging upper gastrointestinal malignancy improved the overall accuracy of staging. Although this may have future implications for the selection of patients for multimodality treatment, management decisions are currently based on laparoscopic findings, which in this study resulted in a resection rate of 97 per cent.

Accurate staging of upper gastrointestinal malignancy is essential if patients are to receive optimal treatment and to ensure maximal use of resources. Unfortunately conventional imaging with ultrasonography and computed tomography (CT) is not always accurate in the staging of patients with gastro-oesophageal cancer[1–4]. Many studies[5–9] report a high incidence of tumours that are found to be irresectable at the time of surgery. These patients may have been more appropriately treated with non-operative palliative measures, which in many cases can provide a good quality of life[10–12]. A recent report[13] has highlighted the benefits of laparoscopic evaluation of patients with gastro-oesophageal cancer; however, laparoscopy alone does not allow a full evaluation of the tumour without trial dissection, which may compromise the feasibility of a future *en bloc* resection. The combination of laparoscopy and ultrasonography may give additional benefits as it allows direct contact between the ultrasonographic probe and the organ of interest, enabling the use of high-frequency ultrasound with high resolution[14]. Previous authors[15,16] have reported the use of laparoscopic ultrasonography in the evaluation of pancreatic tumours and the biliary tree. Results of laparoscopic ultrasonography in the staging of patients with upper gastrointestinal cancer are reported and compared with those of more conventional staging modalities, to determine the accuracy of laparoscopic ultrasonography in staging upper gastrointestinal cancer.

Patients and methods

Patients

Between January and November 1995, 44 patients with a diagnosis of lower-third oesophageal cancer or gastric malignancy were staged according to a standard protocol This involved full blood count, liver function tests, chest radiography, endoscopy (and biopsy) of the upper gastrointestinal tract, abdominal ultrasonography and dynamic contrast-enhanced CT of the chest, mediastinum and upper abdomen. The CT protocol involved contiguous 10-mm collimated sections from the sternal notch to the inferior border of the liver. Intravenous contrast was commenced at the level of the tracheal bifurcation, using 100 ml iopamidol 370 (Merck Pharmaceuticals, West Drayton, UK): 40 ml at 2 ml/s and 60 ml at 0·5 ml/s. Oral contrast, 300 ml 2 per cent Gastrografin (Schering Health Care, Burgess Hill, UK), was administered before the examination. The results of the staging investigations were reviewed by one consultant radiologist (S.C.) and the consultant surgeon in charge of the case (K.G.M.P.) and the details were recorded prospectively. Thereafter each patient was examined with laparoscopic ultrasonography and the staging was modified accordingly. The final diagnosis in each patient is shown in *Table 1*.

Laparoscopic ultrasonography

Laparoscopic ultrasonography was performed as a separate procedure under general anaesthesia. Both surgeons involved were experienced endoscopic surgeons but had little experience of ultrasonography and therefore the images were interpreted by a consultant radiologist (S.C.), who had considerable experience in gastrointestinal and endoscopic ultrasonography and was

Table 1 Final histological diagnosis of tumour in 44 patients with upper gastrointestinal cancer investigated with laparoscopic ultrasonography

	No. of patients
Lower-third oesophageal tumour (proximal extent of tumour below carina)	
Squamous	6
Adenocarcinoma	15
Small cell carcinoma	2
Recurrent carcinoma	1
Gastric adenocarcinoma	
Gastro-oesophageal junction	12
Antrum	5
Linitis plastica	1
Other gastric tumour	
Lymphoma	1
Leiomyosarcoma	1

Paper accepted 23 June 1996

present at each operation. An Aloka (Tokyo, Japan) 7·5-MHz rigid linear array probe was used in all patients. A 10-mm cannula was inserted at the umbilicus using a blunt technique and a pneumoperitoneum was induced with carbon dioxide A 0° laparoscope was then inserted and the peritoneum was inspected. Further 10-mm cannulas were inserted in the right and left sides of the abdomen to allow insertion of the ultrasonographic probe and grasping forceps or suction irrigation probes Any free fluid was aspirated for cytological analysis and peritoneal deposits were biopsied. Using the forceps in the right port, the liver was retracted in a cephalad direction and the anterior surface of the stomach was inspected. The ultrasonographic probe was then inserted through the left port and used to scan the stomach, liver and biliary tree.

The probe was moved to the right port and again the liver and porta hepatis were examined. Care was taken to scan both lobes of the liver and to identify the right and left hepatic veins and the portal confluence. Unless these anatomical landmarks were identified the examination was noted as incomplete. Abnormalities seen within the liver were biopsied if there was suspicion of malignancy. The probe was then brought back across the stomach and lesser curve, the aorta was visualized with any anterior lymphadenopathy and the coeliac axis was inspected. Care was taken to identify the left gastric artery. The probe was inserted into the lesser sac through the lesser omentum, to allow inspection of the posterior surface of the stomach and also to assess the degree of fixation of the tumour.

Nodes greater than 8 mm in maximum diameter were generally regarded as being positive for metastatic tumour. Other ultrasonographic features used to diagnose nodal metastasis were the loss of the normal internal hyperechogenicity and loss of the normal oval shape of lymph nodes Involved nodes tended to be rounder in appearance. When examining the primary tumour, initial laparoscopic inspection identified serosal involvement. Laparoscopic imaging was used to identify the five ultrasonographic layers of the bowel wall described previously[17], to assess earlier tumours.

At the end of the examination the pneumoperitoneum was released through the trocars before their removal.

Laparotomy

Surgical exploration was carried out within 3 weeks of completion of staging investigations. At this time the extent of the local tumour was determined and the degree of fixation to adjacent organs was assessed. The liver and the peritoneal cavity were carefully inspected and palpated. Final staging was according to the Union Internacional Contra la Cancrum tumour node metastasis (TNM) system[18].

Invasion through the wall of the stomach or oesophagus was determined on the resected pathological specimen. Lymph nodes from each compartment were also dissected from the specimen for separate histological analysis These findings were correlated with the results of conventional staging and laparoscopic ultrasonography.

Statistical analysis

The accuracy of laparoscopic ultrasonography and conventional staging in the assessment of the primary tumour, lymph nodes and hepatic metastases was determined and compared with the pathological staging using a paired McNemar's χ^2 test.

Results

Laparoscopy was performed in all patients but inspection was incomplete in five because of the presence of adhesions from previous surgery. Median operating time was 30 (range 15–65) min and there was one minor complication of port-site haematoma, which did not require any treatment. Patients were allowed to eat after recovery from the anaesthetic and all were fully ambulant on the evening of the procedure.

Resection

Nine patients did not undergo resection following laparoscopic ultrasonography. In five patients this was because of advanced disease: four patients had malignant ascites with peritoneal metastases, one of whom also had hepatic metastases, and one further patient had liver metastases that were not detected with conventional imaging techniques. One elderly man was found to have a more locally advanced tumour than was apparent on CT and it was decided not to proceed to thoracolaparotomy. One other patient tolerated a pneumoperitoneum and general anaesthetic so poorly that it was judged unwise to proceed to a major operation despite the tumour being potentially resectable. Two patients are currently receiving neoadjuvant chemotherapy within a controlled trial and will be further evaluated before resection. Thirty-five patients have undergone surgery with the aim of resection and this has been achieved in 34; there was one death within 30 days. In 30 patients there was no evidence of macroscopic or microscopic tumour after resection (R_0), in three there was microscopic evidence of tumour at the resection margins (R_1) and in one patient there were macroscopic peritoneal deposits remaining after resection (R_2).

The only patient found to have an irresectable tumour underwent thoracoabdominal exploration for delayed gastric emptying 18 months after oesophageal resection for adenocarcinoma. Preoperative staging and laparoscopic ultrasonography had shown no evidence of recurrent tumour but at the time of surgery large tumour plaques were identified in the right pleural cavity and adherent to the intrathoracic stomach. The patient who died had a more extensive intrathoracic tumour than had been apparent before operation. Transhiatal oesophagectomy resulted in heavy blood loss at the time of the procedure and the patient suffered a myocardial infarction and cardiac arrest in the postoperative period.

Pathological correlation

Primary tumour. In 14 patients with resected lower-third oesophageal cancer laparoscopic ultrasonography was used to assess extension of the primary tumour into the stomach and around the hiatus. Involvement of the fundus of the stomach was confirmed histologically in two of 14 patients. CT detected this in one patient; in addition there was one false-positive CT result. Laparoscopic ultrasonography detected fundal involvement in one patient and was unable to visualize the fundus adequately in the other patient because of a large hiatus hernia.

Table 2 shows a comparison of the accuracy of laparoscopic ultrasonography and conventional staging for the T stage of the 22 patients with resected tumours involving the stomach. There were five patients in whom endoscopy and biopsy suggested early gastric cancer; in none of these was the primary lesion visualized on CT and all were regarded as having early gastric cancer. In only one was this confirmed histologically in the resected specimen. Laparoscopic ultrasonography was unable to visualize the true case of early gastric cancer but in the other four suspected cases it revealed more extensive invasion through the stomach wall.

In one patient there was direct invasion of a tumour into the liver, pancreas and transverse colon; this was clear at laparoscopy and laparoscopic ultrasonography but was not apparent on CT. There were two patients in

Table 2 Accuracy of laparoscopic ultrasonography and conventional staging investigations in the assessment of primary tumour stage in lesions involving the stomach

Primary lesion	Histology	Laparoscopic ultrasonography	Conventional staging*
Limited to gastric wall ($T_{1,2}$)	4	2	3
Invades serosa (T_3)	16	16	10
Invades adjacent organs (T_4)	2	2	1
Accuracy	0	20 of 22 (91)	14 of 22 (64)
No. overstaged	0	2	4
No. understaged	0	0	4

Values in parentheses are percentages. *Includes endoscopy (plus biopsy), ultrasonography and computed tomography. Only the number of correct investigations is shown for laparoscopic ultrasonography and conventional staging

whom CT suggested extensive invasion around the hiatus with involvement of the aorta; this was not confirmed on laparoscopic ultrasonography or at laparotomy. Of the 22 primary tumours that could be visualized with laparoscopic ultrasonography, staging was correct in 20 compared with 14 for conventional investigations ($P<0.01$).

Intra-abdominal lymph nodes. Histology of the 34 resected specimens showed involvement of intra-abdominal lymph nodes in 18 cases. Laparoscopic ultrasonography correctly identified 16 whereas CT demonstrated only five of these. There was one false-positive result with laparoscopic ultrasonography and no false positives with CT. This gives a positive predictive value of 94 per cent for laparoscopic ultrasonography and 100 per cent for CT. There were two false negatives with laparoscopic ultrasonography, in one patient resulting from a large hiatus hernia with nodes along the lesser curvature which could not be well seen and in a second from a combination of obesity and previous surgery which limited the view. The negative predictive value of laparoscopic ultrasonography was 88 per cent compared with 52 per cent for CT. *Table 3* compares the accuracy of laparoscopic ultrasonography and CT for the assessment of intra-abdominal lymph nodes. The accuracy of CT was 62 per cent and that of laparoscopic ultrasonography was 91 per cent ($P<0.05$).

Hepatic metastases. Inspection of the liver was incomplete in five patients because of the presence of adhesions from previous surgery. In the remaining patients the presence of liver metastases suspected on CT or ultrasonography was confirmed in two patients. In one of these patients, however, it was not possible to visualize a metastasis in segment VIII, identified on CT, as it proved impossible to manipulate the rigid probe into a suitable position. In one other patient a 7-mm metastasis was seen on laparoscopic ultrasonography but was not visualized with other staging modalities. In each case laparoscopic guided biopsy was used to confirm the presence of liver metastases. Two patients were thought to have liver metastases on CT and conventional ultrasonography but on laparoscopic ultrasonography were found to have benign pathology (liver cysts and a haemangioma).

Table 3 Comparison of laparoscopic ultrasonography and computed tomography in the assessment of intra-abdominal lymph nodes in patients with upper gastrointestinal cancer

	Histology	
	Positive	Negative
Computed tomography		
Positive	5	0
Negative	13	16
Laparoscopic ultrasonography		
Positive	16	1
Negative	2	15

Intraperitoneal metastases. In four patients the presence of ascites was demonstrated on laparoscopy; this had been suggested in one patient by CT or ultrasonography. In addition, peritoneal deposits were demonstrated in the pelvis of one patient who had received preoperative chemotherapy with demonstrable shrinkage of a primary gastric tumour that had previously been fixed to the pancreas. However, both laparoscopic ultrasonography and conventional imaging failed to demonstrate the presence of tumour studs in the lesser sac, which were evident at the time of resection.

Miscellaneous lesions. One patient had a large tumour of the ascending colon visualized on both CT and barium enema examination, in addition to the gastric cancer. Despite careful inspection at laparoscopy and laparoscopic ultrasonography it was not possible to demonstrate what subsequently turned out to be a large colonic tumour. In one other patient laparoscopic ultrasonography demonstrated a mucocele of the gallbladder that was not visualized on CT or conventional ultrasonography.

Discussion

The value of laparoscopic evaluation of upper gastrointestinal cancer has been demonstrated previously[13]. Furthermore, in hepatobiliary tumours the addition of high-frequency high-resolution ultrasonography to laparoscopy has led to better staging and patient selection for resectional surgery[15,16]. In this series the addition of laparoscopic ultrasonography to conventional imaging resulted in seven of 43 patients who would have been regarded as having resectable disease, by ultrasonography and CT, being excluded from operation. This was because of peritoneal deposits (four patients), liver metastases (one) and extensive local disease (one). In addition, one patient was excluded after poor tolerance of a general anaesthetic. The exclusion of these patients resulted in a resection rate of 97 per cent (34 of 35 patients) with one perioperative death. This is in contrast to a 79 per cent resection rate if all patients thought to have resectable disease after conventional staging had proceeded to laparotomy. In each of these patients the presence of advanced disease was identified on laparoscopy alone; no further patient was excluded from surgical exploration on the basis of laparoscopic ultrasonography. However, laparoscopy alone is poor at demonstrating the presence of lymph node metastases and the stage of the primary tumour[13,19]. In this series a combination of endoscopy, CT and transabdominal ultrasonography correctly staged 64 per cent of the primary tumours in patients with gastric malignancy or lower-third oesophageal tumours extending into the gastric fundus. Similar results for CT have been found in other centres[1–4]. Laparoscopy and laparoscopic ultrasonography improved the accuracy of T staging in these patients to 91 per cent. Similarly, the accuracy of CT in identifying positive intra-abdominal lymph nodes was 62 per cent compared with 91 per cent for laparoscopic ultrasonography. Although it is clear that the addition of laparoscopic ultrasonography significantly improved T and N staging of patients with gastro-oesophageal tumours, at present this contributes little to the management of these patients. It has been proposed, however, that neoadjuvant chemotherapy should be targeted to patients with stage III and IV disease[20]. To date conventional imaging has made preoperative assessment of patients for neoadjuvant chemotherapy unreliable. However, laparoscopic ultrasonography may allow improved patient selection for such treatment.

There were two patients in whom the combination of laparoscopic ultrasonography and conventional staging failed to identify the advanced nature of intrathoracic tumours; in one patient the tumour was not resected and in the other there was a more extensive dissection than was envisaged and this led to the only perioperative death. Perhaps the combination of laparoscopic and endoscopic ultrasonography would allow more thorough assessment of both intra-abdominal and intrathoracic disease in patients with such tumours[21,22].

In the present series laparoscopic ultrasonography required an additional general anaesthetic and a median of 30 min of operating time. As previous studies have found, this procedure was associated with minimal morbidity[13,15,20,23]; however, it does subject the patient to the potential risk of port-site implantation of tumour cells. A number of reports have now described the occurrence of tumour recurrence at laparoscopy port sites[24–26]. In a recent UK postal survey of laparoscopy in intra-abdominal cancer, port-site recurrence was identified in 4 per cent of patients. This was most common in colorectal excisions (12 per cent) and lowest in diagnostic laparoscopy[27]. Similarly, other groups have reported port-site metastases to be most common in the presence of exfoliated cells, i.e. in malignant ascites or where there has been tumour mobilization[24,25]. The addition of ultrasonography to laparoscopy may reduce the potential for port-site implantation compared with other laparoscopic techniques, as less tumour manipulation and minimal dissection are required to obtain adequate staging.

In conclusion, laparoscopic ultrasonography of patients with gastro-oesophageal cancer resulted in accurate staging of these patients. This may allow better selection of patients for multimodality treatments in the future. In the present series, the addition of laparoscopic ultrasonography to conventional imaging techniques resulted in better selection of patients for resectional surgery and a resection rate of 97 per cent.

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British Journal of Surgery 1996, 83, 1429–1432

Oesophagogastrectomy for iatrogenic perforation of oesophageal and cardia carcinoma

D. J. ADAM, A. M. THOMPSON*, W. S. WALKER and E. W. J. CAMERON

*Department of Thoracic Surgery, City Hospital and *Department of Surgery, Western General Hospital, Edinburgh, UK*
Correspondence to Mr D. J. Adam, Department of Vascular Surgery, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW, UK

A casenote review identified 18 patients with carcinoma of the oesophagus and gastric cardia who underwent transthoracic oesophagectomy after instrumental perforation. Oesophagectomy was performed within 48 h in ten patients (early surgery group) and after a median delay of 22 (range 5–48) days in eight patients (delayed surgery group). All patients underwent resection via left thoracolaparotomy with immediate intrathoracic anastomosis using the stomach in 17 of 18 patients. There were no anastomotic leaks. Significant postoperative complications occurred in five of ten of the early group with two in-hospital deaths and a mean survival of 551 days. Six of eight patients in the delayed group developed postoperative complications with two in-hospital deaths and a mean survival of 297 days. Transthoracic resection with immediate intrathoracic anastomosis can be performed without anastomotic leakage but there is high associated respiratory morbidity. The timing of oesophagectomy has little effect on hospital morbidity or mortality rates but early surgery is associated with better long-term survival.

The mortality rate for iatrogenic oesophageal perforation associated with carcinoma is more than twice that for benign disease[1] and higher than that for normal oesophagus[2]. In such circumstances, oesophagectomy offers the only hope of survival and cure as the perforation is unlikely to heal with conservative management[3] or simple repair[4]. Most surgeons perform oesophagectomy within 24 h as delay beyond this is said to be associated with higher morbidity and mortality rates[2,5,6]. However, the best method of oesophagectomy (transhiatal or transthoracic), the extent of resection and site of anastomosis (intrathoracic[7–9] or cervical[4,10]) and the optimal time to restore intestinal continuity, whether immediate[4,7,8,10,11] or delayed[4,5,12,13], continue to stimulate debate.

A retrospective study was undertaken to audit the authors' experience over the previous decade to determine future policy in terms of operative approach and timing of surgery. This series represents, to their knowledge, the largest reported experience of resectional therapy for perforated carcinoma of the oesophagus and gastric cardia from a single surgical unit.

Patients and methods

Over the 10-year period from January 1983 to December 1992, 597 patients underwent resection for carcinoma of the oesophagus or gastric cardia in the Thoracic Surgical Unit, City Hospital, Edinburgh. During this time, 18 patients (3 per cent) underwent oesophagectomy with immediate reconstruction following instrumental perforation of the thoracic oesophagus. Six patients sustained perforation in another unit and were transferred for resection. Perforation was due to attempted dilatation of a malignant stricture in 12 of the 18 patients, attempted pulsion intubation in three and diagnostic rigid oesophagoscopy and biopsy in three. Perforations that were not diagnosed immediately were located radiologically by contrast swallow. All perforations occurred just proximal to or within the area of the carcinoma.

Among the ten women and eight men, the median age was 65 (range 48–83) years and ten patients had significant pre-existing cardiorespiratory disease (*Table 1*). No patient had received preoperative radiotherapy or chemotherapy.

Ten patients (early surgery group) underwent oesophagectomy within 48 h of perforation, nine of whom underwent operation within 24 h. Perforation was diagnosed immediately in three patients who proceeded to surgery without delay. The diagnosis was delayed in the remaining patients; the mean interval from perforation to surgery was 10 h for the nine patients who underwent oesophagectomy within 24 h.

Eight patients were managed conservatively with gastrointestinal rest, intravenous fluid and antibiotic therapy and closed tube thoracostomy (delayed surgery group) for 5, 6, 19, 21, 23, 26, 26 and 48 (median 22) days before surgery. All patients had their perforations diagnosed on the day of perforation. Four patients were diagnosed and managed in other units and transferred for resection once their clinical status had improved.

Results

Pathology

Squamous cell carcinoma was present in ten patients and adenocarcinoma in eight. Local lymph node metastases (N_1) were present in seven patients with distant nodes (N_2) involved in two. Tumours were staged by the American Joint Committee on Cancer guidelines[14]; stage IIA, IIB, III and IV disease was present in seven, one, eight and two patients respectively. One patient who underwent total oesophagectomy with cervical anastomosis for a tumour in the proximal third of the oesophagus had pathological evidence of residual tumour at the margins of resection.

Surgical technique

All patients underwent resection via single-stage left thoracolaparotomy. One patient required additional right thoracotomy and pneumonectomy to resect an oesophageal lesion invading the right main bronchus and a synchronous squamous carcinoma of the right lower lobe of the lung. The thoracic oesophagus including the perforated portion was mobilized to at least 5 cm above

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Paper accepted 10 June 1996

Table 1 Patient demography

Age	Sex	Pre-existing disease	Histology	Site	Stage	Delay (days)	Complications	Survival (days)
77	F	None	Adenocarcinoma	Distal third	IIB	0	None	377
76	F	IHD, COAD	Squamous carcinoma	Middle third	IIA	0	Cardiorespiratory failure, IPPV 12 days, tracheostomy, chylothorax, AF, inotrope	17
55	M	None	Squamous carcinoma	Distal third	IIA	0	None	1780 (alive)
63	M	COAD	Adenocarcinoma	Cardia	III	0	None	139
66	M	COAD, steroid therapy	Adenocarcinoma	Distal third	IIA	0	Tracheostomy	436
82	F	None	Adenocarcinoma	Distal third	IV	0	Respiratory failure, tracheostomy, TPN, IPPV 4 days	39
63	F	COAD	Adenocarcinoma	Distal third	IIA	1	Aspiration, AF, tracheostomy, IPPV 5 days	727 (alive)
48	M	Previous CVA, NIDDM, hypertension	Adenocarcinoma	Distal third	IIA	1	None	1501 (alive)
70	M	Previous CVA	Squamous carcinoma	Distal third	III	1	None	160
72	F	Previous MI, hypertension, AF	Adenocarcinoma	Cardia	III	2	Tracheostomy, AF, inotrope	330
70	M	Previous lung carcinoma, COAD, hypertension	Adenocarcinoma	Distal third	III	5	Inotrope, IPPV 3 days	546
58	F	MVR, AF, warfarin therapy	Squamous carcinoma	Upper third	III	6	Chylothorax, thoracotomy, TPN, IPPV 21 days, inotrope	21
63	F	COAD	Squamous carcinoma	Middle third	IIA	19	AF, upper gastrointestinal haemorrhage	50
65	F	None	Squamous carcinoma	Middle third	IIB	21	Respiratory failure, AF, TPN, IPPV 5 days, tracheostomy, inotrope	415
78	F	None	Squamous carcinoma	Distal third	IIA	23	None	327
63	M	None	Squamous carcinoma	Middle third	III	26	None	545
83	F	None	Squamous carcinoma	Distal third	IV	26	Rib resection, tracheostomy, IPPV 13 days, TPN, pneumonia, sepsis	26
64	M	None	Squamous carcinoma	Middle third	III	48	Tracheostomy	448

IHD, ischaemic heart disease; COAD, chronic obstructive airways disease; CVA, cerebrovascular accident; NIDDM, non-insulin-dependent diabetes mellitus; MI, myocardial infarction; AF, atrial fibrillation; MVR, mitral valve replacement; IPPV, intermittent positive pressure ventilation; TPN, total parenteral nutrition

the upper limit of the tumour, taking regional lymph nodes and contents of both pulmonary ligaments *en bloc*. The stomach was mobilized by division of the short gastric vessels, then distally outwith the gastroepiploic arcade preserving omentum for an anastomotic wrap. The left gastric vessels were divided at the upper border of the pancreas and all associated coeliac and left gastric pedicle lymph nodes were taken with the operative specimen. No patient required wedge resection of liver or lung or splenectomy or partial pancreatectomy to achieve macroscopic tumour clearance. The pylorus was dilated digitally or with Hegar's dilators. Stomach was used to restore intestinal continuity in all cases. One patient with squamous carcinoma of the upper third of the oesophagus underwent total oesophagectomy with cervical anastomosis. Subtotal oesophagectomy with anastomosis at or above the aortic arch was performed in 14 patients with five middle-third and nine distal-third lesions. Oesophagogastrectomy was performed in three patients for one distal-third oesophagus and two cardia lesions. The anastomosis was performed with either a single-layer (ten patients) or two-layer (three) handsewn technique, or with a stapling device in five patients.

Mean operative blood loss was 410 (range 100–1250) ml for those undergoing surgery within 48 h and 1088 (range 200–2650) ml for those in the delayed group. Mean transfusion requirement was 495 (range 0–2400) ml for the early group compared with 1629 (range 0–3950) ml in the delayed group.

Complications and survival

None of the 18 patients had clinical or radiological evidence of anastomotic leakage. Five patients in the early surgery group and two in the delayed surgery group had no postoperative complications. However, the incidence of respiratory complications was high with seven of 18 patients requiring ventilatory support (mean 9 (range 4–21) days), of whom five required tracheostomy and four died. Tracheostomy was performed in another three patients to allow bronchial toilet without ventilation. Five patients required inotropic support and four received total parenteral nutrition. Chylothorax occurred in two patients: one of these was managed conservatively and the other underwent repeat thoracotomy but both patients died after 17 and 21 days respectively. Median in-patient stay was 16 (range 6–42) days. The overall in-hospital mortality rate was 22 per cent (four of 18 patients).

All 14 survivors were able to swallow on discharge home, and ten had no further dysphagia. One patient required four dilatations for benign stricture. Three patients underwent dilatation for recurrent disease and two proceeded to pulsion intubation. No patient was given postoperative adjuvant therapy.

Among the ten patients who underwent early surgery there were two in-hospital deaths. Two patients died from recurrent disease and one from an unknown cause within the first year. Two died from recurrent disease within the second year. Three patients who were resected for stage IIA disease are still alive with no evidence of disease recurrence at 24, 49 and 58 months after surgery. The mean survival for the group is 551 (range 17–1780) days.

There were two in-patient deaths in the eight patients who had surgery delayed for more than 48 h. Two patients died within the first year, one from recurrent disease and the other after admission to another hospital with an acute abdomen. Four died within the second year after surgery, three with recurrence and one from an unknown cause. Mean survival for this group was 297 (range 21–546) days.

Discussion

Oesophagectomy for iatrogenic perforated carcinoma is uncommon, accounting for only 3 per cent of all resections for carcinoma in this unit.

Even in a contaminated operative field, it was possible to perform immediate intrathoracic oesophagogastrostomy, as used in the majority of elective resections in this unit, without anastomotic leakage. Palliation of symptoms was excellent with all 14 survivors discharged home and able to swallow. Two of 18 patients are alive and free from disease over 4 years after surgery: comparable with the authors' overall 5-year survival rate of 16 per cent for all resected patients and with other publications reporting long-term survival[8,10,11,15]. Left thoracolaparotomy with intrathoracic anastomosis does not result in an increased incidence of anastomotic leakage or provide poor tumour clearance[10]. Only one patient, with carcinoma of the proximal oesophagus, had residual tumour at the margins of resection despite undergoing total thoracic oesophagectomy with a cervical anastomosis. None of the five patients with mid-oesophageal tumours had an incomplete resection. More extensive mobilization and resection, for example by transhiatal[4] or thoracoabdominal approach[10] with immediate cervical anastomosis, does not provide better operative exposure and would have little prospect of providing better palliation or long-term survival. Furthermore, although oesophageal exclusion and two-stage reconstruction is a useful technique in certain circumstances, for perforated carcinoma[4] it provides poor palliation of symptoms compared with immediate reconstruction.

In this series, early resection with two-field lymphadenectomy was associated with less operative blood loss and a lower transfusion requirement than delayed resection or transhiatal oesophagectomy without lymphadenectomy for perforations of benign disease[4]. Postoperative morbidity was high: five of ten undergoing early oesophagectomy and six of eight undergoing delayed resection experienced significant complications. Respiratory complications were particularly common and probably related to acute intrathoracic pathology and thoracotomy in the presence of co-existing cardiorespiratory disease and carcinoma. While early transhiatal oesophagectomy may be associated with a lower incidence of postoperative complications for perforations of benign disease[4], the mortality rate in the present series compares favourably with that reported elsewhere for benign[4,16–18] or malignant[2,10,19–21] disease regardless of surgical approach. The 30-day mortality rate associated with early or delayed surgery was similar and suggests that the timing of oesophagectomy may not be important for survival of the acute episode, although why early surgery should confer a long-term survival advantage remains uncertain.

The present study describes, to the authors' knowledge, the largest reported series of resections performed for perforated oesophageal and cardia carcinoma in a single surgical unit. Despite this, the number of patients studied is too small to make valid statistical conclusions. However, this study has demonstrated that transthoracic oesophagectomy with immediate intrathoracic anastomosis can be performed with low blood loss and without anastomotic dehiscence. Although associated respiratory morbidity is high, the mortality rate is comparable to that for transhiatal or transthoracic oesophagectomy with cervical anastomosis, and the procedure gives excellent palliation of symptoms with the prospect of long-term survival comparable to that for uncomplicated cases of carcinoma. The same surgical technique can be used for perforated carcinoma as for elective resection. There is no place for postponing surgery or delayed reconstruction which provides poor palliation.

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British Journal of Surgery 1996, 83, 1433–1440

Proximal pancreatoduodenectomy for chronic pancreatitis

G. N. STAPLETON and R. C. N. WILLIAMSON

Department of Surgery, Hammersmith Hospital and Royal Postgraduate Medical School, Du Cane Road, London W12 0NN, UK
Correspondence to Professor R. C N. Williamson

A personal series is reported of 52 patients who underwent proximal pancreatoduodenectomy for severe chronic pancreatitis between 1979 and 1994. There were 13 women and 39 men of median age 42·2 (range 12–70) years. Disease predominantly affected the head of pancreas, with calcification present in 37 patients. Indications for operation were chronic pain (47 patients), obstructive jaundice (19) and duodenal stenosis (six); cancer was suspected in 12. In addition, 14 patients had a pseudocyst, two pancreatic endocrine failure and 20 exocrine failure. Aetiology was chronic alcohol abuse in 34, recurrent acute pancreatitis in five and unknown in 13. Pylorus-preserving proximal pancreatoduodenectomy was performed in 45 patients, while the remaining seven had partial gastrectomy. Drainage of a dilated distal pancreatic duct by side-to-side pancreaticojejunal anastomosis was included in 15 patients. Mean operating time was 6·2 (range 4·5–9·5) h and mean blood loss was 2·7 (range 0·2–13·0) litres. There were no hospital deaths, but three patients required a second operation and five had percutaneous drainage of infected collections. During a median follow-up of 54 months, six patients required completion distal pancreatectomy for renewed pain and four others had persistent pain. Four patients required intervention for stricture at the biliary–enteric anastomosis. Ten patients have died from causes not directly related to chronic pancreatitis. Proximal pancreatoduodenectomy is a relatively safe procedure, effectively palliating pain in 80 per cent of patients with chronic pancreatitis.

Management of intractable pain is the greatest challenge posed by chronic pancreatitis. Increasing doses of narcotics add the problem of drug dependency to a group of patients many of whom are already addicted to alcohol. Although the pathogenesis of the pain is poorly understood, control measures are based on the premise of hypertension in the pancreatic duct and parenchyma or inflammatory neuritis in the pancreas itself and surrounding tissues. The ideal interventional procedure would provide long-term analgesia with minimal operative risk and without aggravating pancreatic dysfunction, but this ideal is elusive.

Pain relief with coeliac plexus blockade is generally transient at best[1], and surgical denervation procedures are seldom practised nowadays. Endoscopic manoeuvres, such as pancreatic sphincterotomy and stenting with or without extracorporeal shockwave lithotripsy[2,3], may help selected patients with isolated stricture and duct calculi, but they may be less appropriate in those with extensive fibrosis and calcification. Operative drainage of a dilated pancreatic duct and/or pseudocyst is both safe and effective[4,5], but in the authors' experience barely one-third of patients present a suitable 'target' for drainage. Resectional surgery carries a greater operative risk and may precipitate diabetes and steatorrhoea; it should be reserved for those with severe disease who are unsuitable for any drainage procedure. Total pancreatectomy must be considered when all else fails[6–8], but in patients with residual endocrine function partial pancreatectomy tailored to the maximal site of disease is often the best option[9–11].

Recent years have seen a trend towards resection of the head of the pancreas when this is involved in an inflammatory mass. Complications of chronic pancreatitis such as bile duct stricture, duodenal stenosis and portal vein compression are additional indications. Duodenum-preserving resection of the head of the pancreas (DPRHP) and the Frey variant of this procedure[12–14] are superficially attractive because of the limited number of anastomoses required, but retention of the duodenum as an endocrine organ is of unproven value[15]. The advantage of pancreatoduodenectomy over duodenum-preserving resection is that the procedure is appropriate for benign or malignant disease (the differential diagnosis may be extremely difficult)[16–18] and so it is familiar to all pancreatic surgeons. Preservation of the pylorus should reduce the physiological deficit associated with the classical Whipple resection which incorporates a distal gastrectomy[19–24].

The results of pancreatoduodenectomy in a personal series of 52 patients with chronic pancreatitis support the use of this major operation for those with severe disease of the pancreatic head; the pylorus was preserved in all but seven patients.

Patients and methods

Patients

Between November 1979 and November 1994, a consecutive series of 52 patients received proximal pancreatoduodenectomy for severe chronic pancreatitis under the care of the senior author at the Bristol Royal Infirmary ($n = 12$) or the Hammersmith Hospital, London ($n = 40$). There were 13 women and 39 men of mean age 42·2 (range 12–70) years. Patients who had either completion proximal pancreatectomy after previous distal resection ($n = 16$) or one-stage total pancreatectomy ($n = 17$) were excluded from the series and are reported elsewhere[8]. The operative technique of pancreatoduodenectomy with or without gastrectomy has been described previously[25–27].

Investigations

The pancreas was imaged in all patients by ultrasonography and contrast-enhanced computed tomography (CT); in recent years spiral CT has yielded improved imaging. Biliary and pancreatic ductal anatomy was delineated by endoscopic retrograde cholangiopancreatography (ERCP) in 42 patients, while four had

Presented to the 75th Annual Meeting of the Association of Surgeons of Great Britain and Ireland in London, UK, June 1995
Paper accepted 24 December 1995

percutaneous transhepatic cholangiography. The usual reason for not carrying out ERCP was technical failure because of duodenal stenosis, previous Pólya gastrectomy or distortion by a pseudocyst. Selective coeliac and superior mesenteric angiography with both arterial and venous phases was carried out in 34 patients to identify vascular abnormalities and determine whether there was inflammatory encroachment or occlusion of the great veins[28]. Seven patients had barium meal radiography to investigate the cause of vomiting. The pancreatic ductal tree was further evaluated by intraoperative pancreatography in 25 patients, generally by retrograde cannulation of the duct at the point of transection in the neck of pancreas[29]. Retrograde ductography was indicated particularly when ERCP had failed to demonstrate the upstream duct because of distortion or stricture of the duct in the head.

Endocrine function was assessed by a standard 75-g oral glucose tolerance test (OGTT), and exocrine function was estimated by the pancreolauryl test (normal above 30 per cent)[30] or, in three patients, by measuring 3-day faecal fat content (normal below 15 mmol/day). Immediately before discharge from hospital, the pancreolauryl test was repeated in 35 patients and the OGTT in 43 The glucose tolerance curve, derived from venous plasma samples, was classified according to World Health Organization criteria as normal if fasting and 120-min levels were both less than 7·8 mmol/l; impaired if fasting level was greater than 7·8 mmol/l and 120-min level between 7·8 and 11·1 mmol/l, and diabetic if fasting level was greater than 7·8 mmol/l and 120-min level above 11·1 mmol/l[31].

Follow-up

Follow-up information was derived from the hospital notes of patients still attending the outpatient clinics, from letters or telephone calls to referring general practitioners, physicians or surgeons of those no longer attending the hospital, or from letters directly to patients.

Statistical analysis

Student's *t* test was used to compare preoperative and postoperative results of OGTT and pancreolauryl tests, either the two-tailed test for unpaired samples or the one-tailed test for paired samples.

Results

Aetiology

There was a history of long-standing excessive alcohol intake in 34 patients, of whom 28 were men and six women. In addition to alcoholism, two of these had pancreas divisum, one had an annular pancreas and one was found to have a small and unsuspected neuroendocrine tumour within the resected head of pancreas. Chronic inflammation in five patients, one of whom had a choledochal cyst[32], was attributed to recurrent attacks of idiopathic acute pancreatitis. The remaining 13 patients (nine men and four women) did not give a history of excessive alcohol ingestion or have any relevant family history and were regarded as having idiopathic chronic pancreatitis. It was particularly in this group that the suspicion of cancer arose, the presenting feature often being obstructive jaundice.

Clinical presentation (Tables 1 *and* 2)

All but four patients were referred from outside the immediate hospital catchment area by consultant physicians or surgeons and two of the local patients were referred by physicians. Abdominal pain was the predominant symptom, being present in 47 patients (90 per cent). It manifested as either chronic persistent pain or frequent, recurrent attacks of pain requiring hospital admission. Three patients had previously had a coeliac plexus block. Regular daily use of oral narcotic analgesics was documented in 29 patients, while a further 14 required narcotics on an intermittent basis. Obstructive jaundice was the presenting complaint in 19 patients (37 per cent); 15 of these also had pain of varying severity. In five the jaundice was transient, while in five it was relieved before referral by endoscopic stent insertion (three) or cholecystojejunostomy (two). Bile duct stricture was demonstrated in 25 patients, and pseudocysts ranging from 3 to 9 cm in diameter were present in 14; seven had both pseudocyst and bile duct stricture. Calcification was present in the pancreatic head mass in 37 patients (71 per cent), although it was minimal in eight. In six patients vomiting was a prominent symptom, in addition to chronic pain; five had inflammatory duodenal stenosis and one had alcoholic pancreatitis in an annular pancreas[33].

Suspicion of pancreatic cancer was a real concern in 12 patients (*Table 1*). These patients presented with biliary or duodenal obstruction and had a pancreatic head mass but little or no pancreatic calcification (*Fig. 1*). One man had neither pain nor jaundice, but routine blood screen revealed a raised level of alkaline phosphatase; ultrasonography showed dilated bile and pancreatic ducts, and ERCP showed strictures of both ducts.

Sixteen patients had undergone previous upper abdominal operations, including cholecystectomy (eight), cholecystenterostomy (two, one with gastroenterostomy), transduodenal sphincteroplasty (two) and one each of the following: laparotomy and T tube insertion, cholecystostomy, excision of a choledochal cyst, Pólya partial gastrectomy and pseudocystojejunostomy. Three patients had indwelling biliary endoscopic stents and two had had pseudocysts aspirated.

Table 1 Indication for operation in 52 patients who underwent pancreatoduodenectomy for severe chronic pancreatitis

Main indication for operation	No. of patients
Abdominal pain alone	26
Pain and jaundice	15
Painless jaundice	4
Vomiting (and pain)	6
Suspicion of cancer*	1

*The possibility of cancer contributed to the decision for operation in a further 11 patients with either painless jaundice (four patients) or pain associated with jaundice (three), bile duct stricture (two) and duodenal stricture (two)

Table 2 Associated features in 52 patients who underwent pancreatoduodenectomy

Associated feature	No. of patients
Duodenal obstruction	6
Biliary stricture	25
Pseudocyst	14
Calcification	37
Portal hypertension	3

Preoperative pancreatic function

Two patients were already insulin-dependent diabetics at the time of referral. A preoperative OGTT was carried

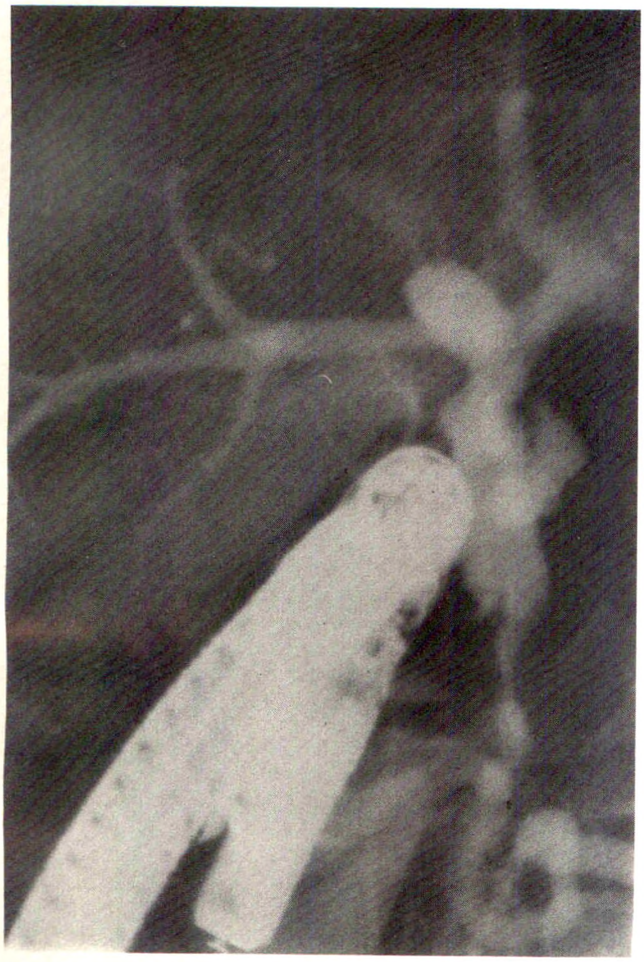

Fig. 1 Endoscopic retrograde cholangiopancreatography in a 30-year-old man who presented with a short history of painless obstructive jaundice. The cholangiogram shows a tight and irregular stricture which was thought to be malignant. The resection specimen confirmed severe (idiopathic) chronic pancreatitis and no evidence of carcinoma. The patient is alive and well 6 years later

out in 43 of the remaining 50 patients. The OGTT was normal in 28 patients, impaired in ten and diabetic in five.

Fourteen patients were taking pancreatic enzyme supplements at the time of referral. Pancreatic exocrine function was measured before operation in 39 patients. Three had 3-day faecal fat measurements and 36 pancreolauryl tests. One faecal fat estimation was below 15 mmol/day, two pancreolauryl tests were completely normal at 65 and 43 per cent, and three were just above normal (30–35 per cent). Three-day faecal fat estimations were abnormal in two, and pancreolauryl ratios were clearly abnormal in 31 patients: ten between 20 and 29 per cent, 11 between 10 and 19 per cent and ten below 10 per cent. Objective evidence of exocrine insufficiency was, therefore, present in 33 of the 39 patients tested, while 20 were considered to have exocrine failure.

Operations

The preferred operation of pylorus-preserving proximal pancreatoduodenectomy (PPPP) was performed in 45 patients (87 per cent) (*Fig. 2*). Mean length of duodenum preserved was 3·9 (range 1·5–5·5) cm. Seven patients had a conventional Whipple resection including partial gastrectomy because of gross duodenal inflammation and stenosis (four), concomitant gastric carcinoma (one)[33], previous Pólya gastrectomy (one) or active duodenal ulceration (one). The standard reconstruction comprised end-to-end pancreaticojejunostomy, end-to-side choledochojejunostomy and end-to-side duodenojejunostomy (or gastrojejunostomy in Whipple operations). The pancreaticojejunostomy was stented with an infant feeding tube in 21 patients with a small duct.

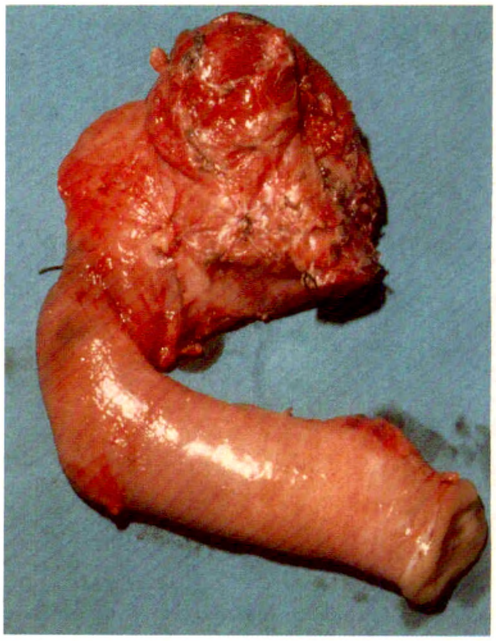

Fig. 2 Operative specimen from a pylorus-preserving proximal pancreatoduodenectomy showing a large inflammatory mass in the pancreatic head in a 45-year-old man with chronic alcoholic pancreatitis

Pancreatography was performed during 25 operations to assess the current state of the duct in the body and tail of the pancreas. In 15 patients with a dilated duct at the neck of pancreas, drainage of the distal gland was combined with resection of the head. Preoperative and/or intraoperative imaging confirmed dilatation of the distal duct (*Fig. 3*), which often contained further calculi. In these patients a modification of the pancreatic anastomosis was performed with a side-to-side anastomosis of the jejunum to the longitudinally incised pancreatic duct (*Fig. 4a*). Mean length of longitudinal pancreaticojejunostomies was 8 (range 5–11) cm.

The gallbladder was not removed routinely; it was preserved in 34 patients (65 per cent). Cholecystectomy had been carried out in the past in eight patients and was included in the operation in ten. In 11 patients the septum between the divided cystic duct and common hepatic duct was slit longitudinally to provide a wider biliary–enteric anastomosis, and in three patients the gallbladder was anastomosed to the jejunum in addition to the choledochojejunostomy to provide an additional biliary outlet when the common bile duct was very small and inflamed (*Fig. 4b*). The biliary–enteric anastomosis was stented with a T tube in 16 patients. No patient with a retained gallbladder developed cholecystitis in the postoperative period, but one was subsequently found to have gallstones.

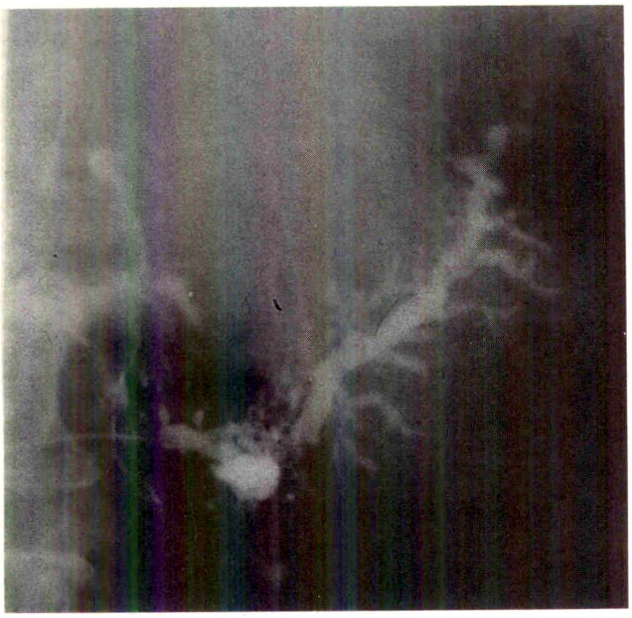

Fig. 3 Retrograde operative pancreatogram obtained by cannulation of the pancreatic duct in the neck of pancreas during proximal pancreatoduodenectomy. There is dilatation of the duct in the body and tail, which was managed by concomitant duct drainage

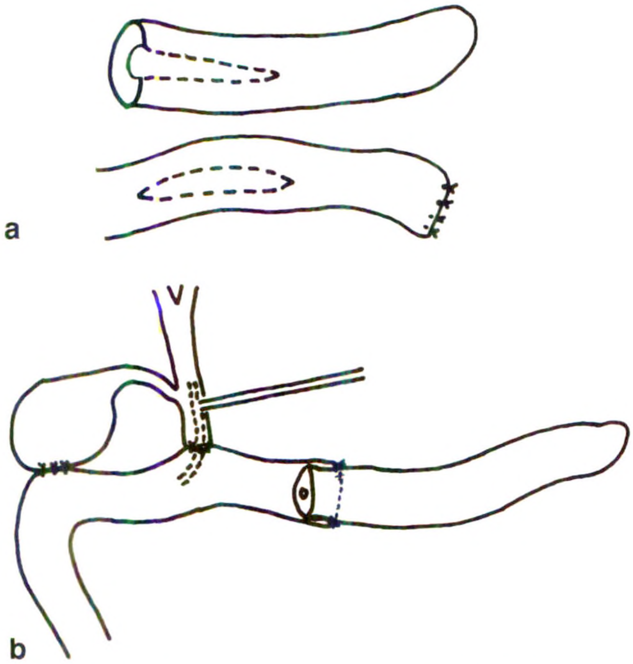

Fig. 4 Additional operative techniques during proximal pancreatoduodenectomy. **a** For a dilated distal pancreatic duct, side-to-side pancreaticojejunostomy is performed after longitudinal incision of the duct. **b** For a tiny thick-walled bile duct, a T tube is used to stent the choledochojejunostomy and a concomitant cholecystojejunostomy is created

Mean operating time was 6·2 (range 4·5–9·5) h and mean blood loss 2·7 (range 0·2–13·0) litres. Mean postoperative hospital stay was 18·3 (range 9–60) days. Twenty-four patients had complications; in these the postoperative stay was 23·9 (range 11–60) days compared with 12·5 (range 9–15) days for those with uncomplicated recovery. Complications included delayed return to normal eating (nine patients), intra-abdominal collections (eight), wound sepsis (ten) and transient leaks from the biliary anastomosis (three) or pancreatic anastomosis (two). One patient had early reoperation for evacuation of a haematoma and five had percutaneous aspiration or drainage of intra-abdominal collections. Two collections comprised amylase-rich fluid and three contained bile. The remaining collections resolved spontaneously with antibiotic treatment (one) or by discharging through the previous drain site (two). Seven of the ten patients with wound sepsis had no other complications, and hospital stay for them was a mean of 16 (range 11–27) days.

Two of those who had delayed return to normal eating had protracted conservative management before being re-explored; both had hold-up not at the pylorus but at the point of transit of the jejunum behind the transverse mesocolon, one because of herniation and one because of adhesions. The other seven had gastric atony. One of these patients who had a Whipple resection for tight duodenal stenosis had had prolonged gastric outlet obstruction before operation. The remaining six (12 per cent) had delayed gastric emptying after PPPP; of these two had associated wound sepsis, one had an intra-abdominal collection (aspirated percutaneously), one had haematemesis on day 10 (settled with omeprazole) and one had had partial gastric outlet obstruction before operation. All patients regained their preoperative weight, and most had improved appetite and body-weight secondary to the relief of pain.

Postoperative pancreatic function

Of 28 patients who had a normal preoperative OGTT, four were not retested after operation, 15 remained normal on postoperative testing, and nine deteriorated (seven impaired, two diabetic). Of ten patients with an impaired preoperative test, three remained impaired after operation while seven improved to normal. Of five patients with a diabetic test before operation, one was not retested, one remained diabetic and three improved (two normal, one impaired). Overall, glucose tolerance deteriorated in nine patients, remained static in 15 and improved in ten. Finally, in seven patients not tested before operation, the postoperative OGTT was normal in four and diabetic in one, while two did not have a postoperative OGTT. Two patients required insulin as an immediate consequence of the resection. The overall results show an increase in fasting blood glucose level as a result of operation, but no significant difference for the 2-h glucose level (*Table 3*). Among the 29 patients with combined preoperative and postoperative data, both mean fasting and 2-h values were higher after proximal pancreatoduodenectomy (*Fig. 5*).

Pancreolauryl tests were carried out after operation in 35 patients (*Table 3*), and all were below 30 per cent; only four were above 20 per cent. Among 23 patients who had repeat tests, exocrine function had deteriorated in 13, improved slightly in eight and remained unchanged in two (*Fig. 6*). Mean postoperative pancreolauryl ratio was significantly lower both overall and among the subgroup of patients with combined preoperative and postoperative data.

On long-term follow-up a further 14 patients became frankly diabetic, requiring insulin (six) or glibenclamide (four). In four the diabetes was a direct consequence of

Table 3 Summary of all pancreatic function tests, both endocrine (oral glucose tolerance test) and exocrine (pancreolauryl test)

	Before operation	After operation	*P**
Fasting glucose			
No. of tests	43	43	
Blood glucose (mmol/l)	5·05(1·15)	5·80(1·58)	0·02
2-h OGTT			
No. of tests	43	43	
Blood glucose (mmol/l)	7·72(2·93)	8·02(4·11)	0·72
Pancreolauryl test			
No. of tests	36	35	
Pancreolauryl ratio (%)	17·81(12·60)	10·81(6·09)	0·005

Values are mean(s.d.). Several patients had either preoperative or postoperative testing but not both. OGTT, oral glucose tolerance test. *Student's *t* test

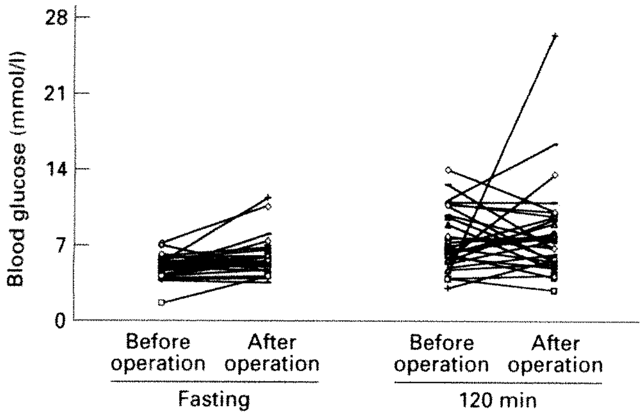

Fig. 5 Oral glucose tolerance tests in 29 patients with both preoperative and postoperative data. Individual values are plotted. Mean(s.d.) fasting blood glucose levels were 4·99(1·10) and 5·78(1·74) mmol/l before and after operation respectively ($P = 0·014$). Respective 120-min levels were 7·53(2·82) and 8·26(4·51) mmol/l ($P = 0·003$)

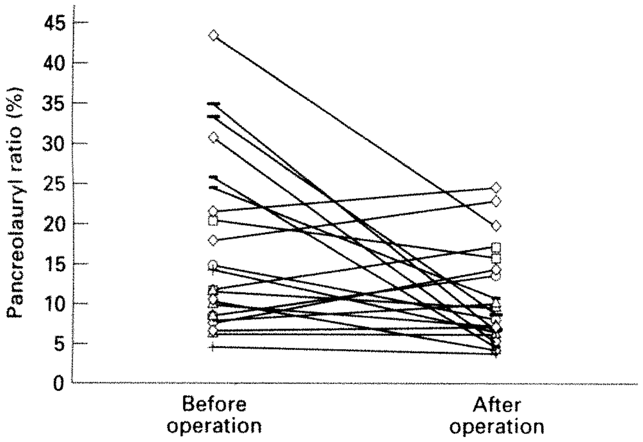

Fig. 6 Pancreolauryl tests in 23 patients with both preoperative and postoperative data. Individual values are plotted. Mean(s.d.) pancreolauryl ratios were 16·93(10·50) and 10·94(5·78) per cent before and after operation respectively ($P = 0·017$)

completion pancreatectomy, but ten deteriorated later after proximal pancreatoduodenectomy alone; of these three had a diabetic curve after operation, but the other seven developed progressive disease. Pancreatic exocrine insufficiency has been much commoner; 42 patients subsequently required pancreatic enzyme supplements to control steatorrhoea. Three of the ten patients who have not taken enzymes had postoperative pancreolauryl ratios below 15 per cent.

Late outcome

Median follow-up is 54 months (range 6 months to 15 years). Of the 47 patients who had pain at presentation, 37 had satisfactory relief of pain; 22 no longer require analgesics, and 15 with some residual pain use non-narcotic analgesics on an intermittent basis. Ten patients still required narcotics after the operation, and six of these have proceeded to completion pancreatectomy at a mean of 28 (range 7–51) months after pancreatoduodenectomy. One had chronic pain due to mesenteric vascular occlusive disease (which required two operations and ultimately led to death), two are addicted to narcotics and have declined completion pancreatectomy, and one has a much lower narcotic requirement.

Among the subgroup of 15 patients with distal duct drainage in addition to proximal resection, 11 have had worthwhile relief of pain, one is addicted to narcotics and three have received completion pancreatectomy.

Four patients developed late stricture of the biliary–enteric anastomosis and required either surgical revision to hepaticojejunostomy (two) or percutaneous dilatation (two). One of the four, who had a small inflamed bile duct at the original operation, had received a gallbladder anastomosis as well as the choledochoenterostomy. One other patient was reoperated on for adhesions at 6 months.

Ten patients have died (*Table 4*), seven from unrelated diseases, one from unknown cause, one from alcoholic liver disease and one from adult respiratory distress syndrome following an operation for strangulated adhesional obstruction of the small bowel.

Table 4 Details of patients who died after pancreatoduodenectomy

Sex	Age at operation (years)	Post-operative survival (months)	Operation	Cause of death
F	37	54	PPPP	Mesenteric vein thrombosis
M	38	90	PPPP	Strangulated obstruction
M	35	100	PPPP	Sudden death from unknown cause
F	42	71	PPPP and completion pancreatectomy	Acute asthma
M	46	38	Whipple	Acute myocardial infarct
M	52	83	PPPP	Oral carcinoma
M	41	84	Whipple	Liver failure
M	52	3	PPPP	Metastasis
M	51	60	Whipple	Bronchopneumonia
M	70	9	PPPP	Congestive cardiac failure

PPPP, pylorus-preserving proximal pancreatoduodenectomy

Discussion

Pancreatoduodenectomy achieved satisfactory relief of symptoms in over 80 per cent of this group of patients who clearly had severe chronic pancreatitis as indicated by the frequency of calcification, pseudocyst, bile duct stricture and duodenal stenosis. This result was achieved without any hospital deaths, but at the cost of a major operation lasting about 6 h and associated with substantial blood loss in several patients and a complication rate of 46 per cent. It is notable that 21 of the 52 patients had had previous pancreatobiliary procedures, either operative or non-operative.

The major advantage of pancreatoduodenectomy over DPRHP is the security of adequately removing a cancer, which was suspected in nearly a quarter of patients in this series and actually coexisted in one of them. In one series, four of 66 patients with a mass in the head of pancreas who were considered for DPRHP required conversion to pancreatoduodenectomy after a malignant tumour was found on frozen-section biopsy[12]. This event occurred in five of 43 patients in another series[34], and it led to the exclusion of one patient from a controlled prospective trial comparing DPRHP and PPPP[35]. From the technical standpoint DPRHP is just as difficult an operation as pancreatoduodenectomy, and it carries its own list of serious complications including (among 128 patients[13]) acute pancreatitis (11 per cent), haemorrhage from the cut surface of the pancreas (9 per cent), failure to relieve biliary obstruction (5 per cent) and ischaemic duodenal necrosis with fistula formation (1 per cent); none of these problems was encountered in the present series. Moreover, in 17 per cent of those with stenosis of the common bile duct, the decompressive effect of resection was inadequate and an additional anastomosis to the distal common bile duct was required[13].

There were small but significant reductions in exocrine and endocrine function after pancreatoduodenectomy, but these were of limited clinical importance since most patients already had preoperative exocrine impairment and only two required insulin as an immediate consequence. The endocrine data are similar to those the authors reported previously in a smaller group of patients[30], but a significant reduction in the pancreolauryl ratio emerges from this larger experience. The incidence of exocrine impairment before operation (85 per cent) was identical to that reported by Beger and colleagues[13] in a similar series of patients with severe inflammation of the pancreatic head, and 100 per cent (97 per cent in Beger's series) of those tested after operation had abnormal exocrine function. It has been claimed that an important advantage of DPRHP over pancreatoduodenectomy is the maintenance of a more physiological control of blood glucose[15]. In a prospective trial with 20 patients in each arm, DPRHP gave better results than PPPP in terms of both pain relief and endocrine function[35], but the analgesic effect of PPPP was surprisingly poor and follow-up was very short and incomplete[36]. The present results show that excision of the pancreatic head is unlikely to precipitate diabetes, in contrast to an equivalent resection of the distal gland[30]. A small proportion of patients became diabetic on long-term follow-up, which accords with the natural history of the disease[13].

The operation failed to abolish pain in ten of 47 patients, but the 12 per cent rate of subsequent completion pancreatectomy is broadly similar to that associated with distal pancreatectomy in the authors' experience. Pancreatoduodenectomy does not have the late attrition rate of total pancreatectomy. Only two deaths in this series could be attributed to the disease or the operation, whereas in an earlier series of total pancreatectomy for chronic pancreatitis, 29 per cent of patients died later from disease-related causes[8]. The 19 per cent death rate at a median of 60 months in the present series is lower than the 34 per cent at 5 years (rising to 46 per cent at 11 years) in a previous series from France[37]. All 50 patients in the French series had alcoholic pancreatitis, and all had a conventional Whipple operation with hemigastrectomy. Continued alcohol abuse was clearly linked with premature death, while several other patients died from smoking-related diseases. These conclusions are supported by a multivariate analysis of 2015 patients with chronic pancreatitis which showed, first, that survival was significantly less than in the background population and, second, that age at diagnosis, smoking and alcohol abuse were predictors of premature death[38].

Because the gastroduodenal artery is divided during pancreatoduodenectomy, particular care must be taken not to devascularize the bile duct by damaging its collateral supply from the right and left hepatic artery[39]. Pericholangitis seen in advanced pancreatitis can make for a difficult biliary reconstruction. In those with a small-diameter bile duct, retention of the gallbladder and division of the septum between cystic duct and common hepatic duct to widen the biliary orifice facilitates the anastomosis and may help to prevent (or circumvent) late biliary–enteric stricture. Although retaining the gallbladder is unconventional, no complications were encountered as a consequence, and this manoeuvre may assist biliary reconstruction in a difficult case. By contrast, pancreatic reconstruction is generally simpler and safer after resection for benign than malignant disease, because the associated fibrosis supports the placement of sutures and the enzyme content of the pancreatic juice is low[27]. Two patients had trivial pancreatic leaks, which presented with collections of juice with a high amylase content and which resolved after percutaneous drainage.

The principle of conservative resection for benign disease, which underlies retention of a healthy gallbladder, extends to preservation of the pylorus and duodenal cap except in the few patients with duodenal ulceration or stenosis. Although postoperative weight gain has been satisfactory, there is little objective proof that PPPP is better than resection including hemigastrectomy. Delayed gastric emptying in the postoperative period was a problem in only six patients with PPPP, and a possible contributory cause (notably sepsis) was found in five of these. Interestingly, one patient with pre-existing outlet obstruction had delayed gastric emptying after conventional Whipple resection. The 12 per cent incidence of postoperative gastric atony compares with widely varying rates of 5–51 per cent in other series of patients with PPPP[24]. Gastric emptying of liquids and solids was investigated isotopically in this laboratory in 24 patients with PPPP and 12 with a Whipple resection at a median of 5 months after operation[24]. Irrespective of the type of operation, liquid emptying was delayed in about 50 per cent of the patients and solid emptying in 60–80 per cent, while attendant symptoms were scarce. Surprisingly, therefore, antrectomy does not seem to prevent gastric atony, although retention of the pylorus protects against duodenogastric reflux.

The onset of obstructive jaundice (or duodenal stenosis) in a patient with painful chronic pancreatitis is a clear indication to consider operation; jaundice in the absence of pain raises the spectre of carcinoma. The importance of a biliary stricture without jaundice is, however, contentious. The early changes of secondary biliary cirrhosis seen in one study of patients with chronic pancreatitis and bile duct stricture[40] were conspicuously absent in another study, in which liver biopsy merely showed evidence of cholestasis[41]. Although further data are required, it would seem unwise to delay operation too long in those with persistently raised levels of liver enzymes in the blood; alcoholic liver disease is surprisingly uncommon in patients with chronic pancreatitis[42].

There is a definite group with chronic pancreatitis whose members are most effectively helped by resecting the head of the pancreas. The authors are not yet convinced about the physiological superiority of DPRHP over PPPP and favour the more complete resection because of the frequent concern about cancer as well as its greater technical simplicity. Finally, if there is extensive distal disease, resection of the head can sometimes be combined with duct drainage in the body and tail. The authors have used retrograde ductography to demonstrate ectasia and calculi in the distal duct, since radiography is more informative than simple probing of the duct; intraoperative ultrasonography might also be valuable in this context. In these patients with advanced disease, even the combination of proximal resection and distal duct drainage can sometimes fail and necessitate completion pancreatectomy.

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British Journal of Surgery 1996, 83, 1441

Surgical workshop

Angled metal cholangiography cannula for laparoscopic cholecystectomy

N. D. KARANJIA, D. BANERJEE and
G. H. DICKSON
Department of Surgery, Worthing Hospital, Park Avenue, Worthing BN11 2OH, UK
Correspondence to: Mr G. H. Dickson

Laparoscopic techniques for peroperative cholangiography are more complex, and only 25 per cent of surgeons perform this procedure either routinely or selectively[1]. This may be because some surgeons find it difficult, time-consuming or expensive.

A simple metal cannula that renders peroperative cholangiography easy during laparoscopic cholecystectomy is described. A similar cannula has been used for open cholecystectomy[2].

Surgical technique

Laparoscopic cholecystectomy is performed using four cannulas. Once the structures in Calot's triangle have been dissected and defined, peroperative cholangiography is carried out with a metal cholangiography cannula (Misco Medical, Thorpe Bay, UK) (*Fig. 1*). This is 28 cm long, has an olive-shaped end with two lateral eyes and has a 45° bend approximately 2·0 cm from the end. It costs UK £25 and it is not reusable. It is inserted into the abdominal cavity through a 14-G, 13-cm angiocath placed between the epigastric and subcostal cannulas. After removing the inner needle, the hub of the angiocath is cut off and, while the surgeon holds the plastic firmly, the metal tip of the cannula is passed through the catheter. It is important to introduce the needle parallel to the grasping forceps holding Hartmann's pouch and to have the angled tip parallel to the cystic duct before cannulation. After incising the cystic duct, it is milked backwards with forceps to remove any small stones. The cannula may then be placed into the cystic duct. A clip is tightly applied just proximal to the olive to hold the cannula in place. The grasping forceps holding Hartmann's pouch may then be removed. The graspers on the fundus of the gallbladder may be left in place and the other cannulas (umbilical and epigastric) may be retracted appropriately. Cholangiography is then performed using an image intensifier.

Paper accepted 10 December 1995

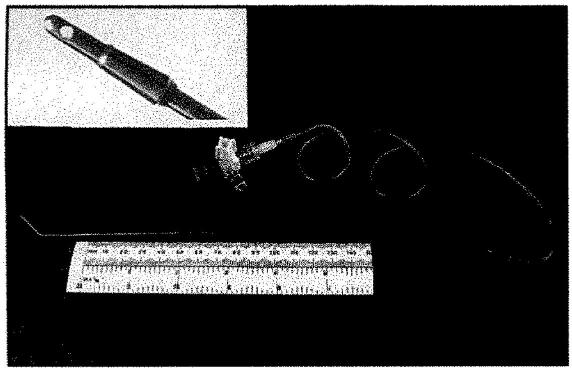

Fig. 1 Misco Medical catheter cholangiography needle

Patients

Data were prospectively collected on 173 consecutive patients undergoing laparoscopic cholecystectomy with routine cholangiography.

A good quality cholangiogram was defined as one showing clear pictures of the cystic duct leading to the confluence of the common hepatic and common bile ducts, with clear views of the right and left hepatic ducts and their sectoral branches, and showing the terminal common bile duct with contrast flowing into the duodenum.

The time taken to perform cholangiography in 43 consecutive patients from clipping the cystic duct at the gallbladder end to clipping the cystic duct at its central end, just before its division, was recorded.

Results

Good-quality peroperative cholangiograms were obtained in 171 (98·8 per cent) of 173 patients; there was slight extravasation of contrast in two patients but, despite this, the pictures were satisfactory. In two patients a cholangiogram could not be obtained as the cystic duct was small and tortuous and could not be cannulated. The mean time for cholangiography was 15·2 (range 9–33) min.

Discussion

Insertion of a cannula into the common bile duct via the cystic duct is the safest method for performing peroperative cholangiography[3]. Most cannulas are flexible and awkward to introduce during laparoscopic cholecystectomy. They often impact on the spiral valve of Heister. At open operation the cystic duct is often gently dilated by a probe and the valve can be broken down. This is more difficult at laparoscopic cholecystectomy and may introduce gas bubbles into the system. One advantage of the metal cannula is that its blunt olive end acts as its own dilator and the cannula usually slips into the cystic duct with ease.

If a flexible cannula is used, the clip holding the cannula within the cystic duct cannot be tightly applied in case the catheter narrows; consequently, there is a risk that the cannula may slip out or that dye may extravasate. The clip used to hold the metal cannula in place may be applied tightly without the prospect of narrowing the cannula; the blunt olive impacts into the clip and prevents extravasation of contrast.

The metal cannula has not been known to cause any injury to the bile ducts in the authors' series. It has made peroperative cholangiography for laparoscopic cholecystectomy a quick and easy procedure which is possible in almost 99 per cent of patients.

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British Journal of Surgery 1996, **83**, 1442–1443

Hepatobiliary anatomy in patients with transposition of the gallbladder: implications for safe laparoscopic cholecystectomy

M. IDU, J. JAKIMOWICZ, A. IUPPA and A. CUSCHIERI*

*Departments of Surgery, Catharina Hospital Eindhoven, The Netherlands, and *Ninewells Hospital and Medical School, University of Dundee, UK*

Correspondence to: Professor A. Cuschieri, Department of Surgery, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK

The surgical anatomy of six patients with sinistroposition of the gallbladder is described. Five of these were encountered in a consecutive series of 1764 patients undergoing laparoscopic cholecystectomy for symptomatic gallstone disease in two hospitals between 1989 and 1994, a prevalence of 0·3 per cent in patients undergoing this operation. Despite the left-sided transposition of the gallbladder, the biliary pain experienced by these patients was always on the right side. Preoperative diagnosis of this anomaly was made in only one of six patients despite routine preoperative external ultrasonography and selective preoperative cholangiography. In sinistroposition the cystic artery always crosses in front of the common bile duct from right to left. The cystic duct may open on the left or right side of the common hepatic duct. The anomaly does not preclude safe laparoscopic cholecystectomy but modifications of the port sites and use of the falciform lift facilitate the procedure in these cases. The anatomical features of the sixth case encountered in a patient undergoing resection of hilar cholangiocarcinoma indicate that sinistroposition of the gallbladder may be due to failure of development of segment IV of the liver.

A left-sided gallbladder is an integral component of situs inversus[1]. In the absence of this condition, abnormal location of this organ is generally recognized as an uncommon anomaly. Thus, in 1964, a collective review of the Western literature yielded only 24 cases of left-sided gallbladder[2]. There have been other isolated reports of the condition since then[3,4]. Two types of gallbladder malposition in the absence of situs inversus have been described by Beck[5]: medioposition of the gallbladder and sinistroposition (transposition). In medioposition, the gallbladder is displaced medially to lie on the undersurface of the quadrate lobe but on the right side of the round ligament. In sinistroposition, the gallbladder lies under the left lobe (usually segment III) to the left of the round ligament. Despite its allegedly rare incidence, the authors have encountered six cases of sinistroposition. The resulting pathological anatomy has implications for the safe conduct of laparoscopic cholecystectomy and is described in this report.

Patients and methods

Five patients (four women) aged 21–42 years presented with episodes of biliary colic; gallstones were confirmed by ultrasonography. In all patients the common bile duct was normal on ultrasonography and preoperative liver function tests showed no abnormality. A preoperative diagnosis of left-sided gallbladder was made on the basis of external ultrasonography in one patient. In these five patients the attacks of colicky abdominal pain were in the classical position, i.e. in the right upper quadrant with radiation to the right back[2]. All patients were scheduled for laparoscopic cholecystectomy without preoperative cholangiography. The procedure was completed satisfactorily in four patients but converted to open cholecystectomy in one because of difficult dissection and bleeding from the cystic artery.

In addition to pain in the right upper quadrant, a sixth patient had clinical jaundice (bilirubin 100 μmol/l), a raised alkaline phosphatase level of 200 units/l and gross dilatation of the intrahepatic biliary tract on ultrasonography. Computed tomography showed an enlarged lymph node near the head of the pancreas. Endoscopic retrograde cholangiopancreatography (ERCP) confirmed the presence of a hilar stricture suggestive of a Klatskin cholangiocarcinoma. This patient was subjected to staging laparoscopy, which confirmed operability of the lesion and revealed transposition of the gallbladder. He was treated by radical resection of the tumour with left hepatectomy as the lesion was extending along the left hepatic duct.

Surgical anatomy

Prevalence. Five of the cases described in this report occurred in a consecutive series of 1764 patients undergoing laparoscopic cholecystectomy for symptomatic gallstone disease between 1989 and 1994, a prevalence of 0·3 per cent in those having this operation.

Liver. All cases were distinguished by a marked, deep and anterior-facing umbilical fissure with an apparent absence of the quadrate lobe of the liver (*Fig. 1*).

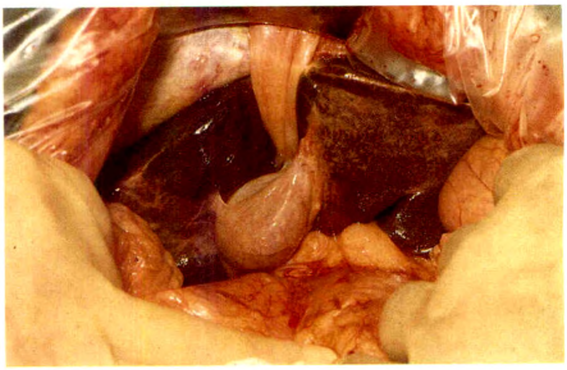

Fig. 1 Intraoperative finding of sinistroposition of the gallbladder in a patient undergoing resection of a hilar cholangiocarcinoma. The gallbladder is situated to the left of the round–falciform ligament complex and is suspended from the medial part of segment III with the fundus adherent to the undersurface of the right lobe. Note the deep anterior umbilical fissure. A segment IV bile duct could not be identified during extended resection including left hepatectomy

Paper accepted 14 January 1996

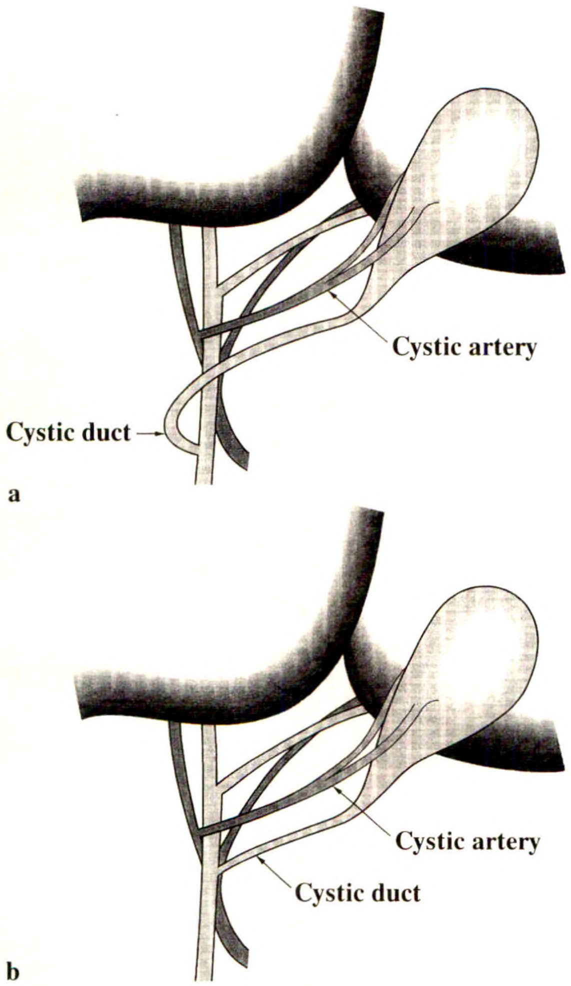

Fig. 2 Distribution of the cystic artery and cystic duct in sinistroposition of the gallbladder encountered in the present series. **a** Cystic duct crosses to join the hepatic duct on the right; **b** cystic duct joins the hepatic duct on the left

Evidence for the latter was confirmed in the patient undergoing radical resection of a Klatskin tumour with left hepatectomy, in whom a segment IV duct could not be identified arising from the left hepatic duct. The disposition of the structures in the porta hepatis of this patient was different from normal: the bile duct was anterior to the common hepatic artery and the portal vein lay behind the artery in the sagittal plane.

Relationship to round ligament. All the gallbladders were to the left of the round ligament and lay beneath segment III of the left lobe (*Fig. 1*).

Hepatoduodenal ligament. This was situated to the right of the round and falciform ligament in five patients and to the left (converted case) in one.

Origin and course of the cystic artery. In all cases the cystic artery was long. It originated on the right side of the common bile duct and coursed to the left in front of the bile duct to the gallbladder (*Fig. 2*).

Termination of the cystic duct. The cystic duct entered the left side of the common bile duct in three patients; in the other three it crossed anterior to the common bile duct before its entry on the right side (*Fig. 2*).

Discussion

On first inspection the transposed gallbladder is inconspicuous as it is overlapped by both the round and falciform ligaments and by the left lobe of the liver. The most useful simple procedure for improving exposure during laparoscopic cholecystectomy is the falciform lift, which lifts the central portion of the liver and moves the ligament off the operative field[6]. Although cholecystectomy can be carried out with the standard port sites, a better arrangement for laparoscopic removal of a left-sided gallbladder consists of more medial positioning of the gallbladder-retracting port and placement of the right-hand operating port well to the left of the midline. To some extent, the long cystic artery and duct facilitate the dissection but this should be kept to the left of the common bile duct and no attempt should be made to trace them to their origins.

Sinistroposition of the gallbladder (left-sided transposition) may not be as rare as generally believed, possibly because it is not recognized at open operation or because of under-reporting. The anomaly is obvious when viewed laparoscopically. Despite routine ultrasonography of the gallbladder in patients undergoing investigation for gallstone disease, diagnosis of the abnormal position is missed in the majority of cases and is not identified by contrast studies including ERCP. Sinistroposition of the gallbladder is probably the result of failure of development of the quadrate lobe of the liver, as suggested by the operative findings in the patient undergoing resection of hilar cholangiocarcinoma with left hepatectomy.

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British Journal of Surgery 1996, 83, 1444–1447

Angiogenesis inhibitor TNP-470 prevents implanted liver metastases after partial hepatectomy in an experimental model without impairing wound healing

H. TANAKA, H. TANIGUCHI, T. MUGITANI, Y. KOISHI, M. MASUYAMA,
H. KOYAMA, M. HOSHIMA and T. TAKAHASHI

First Department of Surgery, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602, Japan
Correspondence to: Dr H. Tanaka

The ability of the angiogenesis inhibitor TNP-470 to prevent liver metastasis after partial hepatectomy, and whether TNP-470 impairs liver regeneration or skin wound healing, was evaluated. Following the injection of VX2 carcinoma cells into the portal vein of rabbits, half of the animals underwent resection of the middle hepatic lobe (hepatectomized group) and half did not (non-hepatectomized group). TNP-470 (50 mg) was infused continuously into the portal vein in both groups for 7 days, while controls received only water. The hepatectomized TNP-470-treated group had significantly fewer tumours (mean(s.e.m.) 23·3(12·3)) than the hepatectomized control group (123·7(24·4)). There was no significant difference in the 5-bromo-2′-deoxyuridine labelling index of regenerated hepatocytes between the TNP-470-treated and control groups. Wound healing in TNP-470-treated animals was not impaired. Intraportal infusion of TNP-470 prevents the recurrence of liver metastasis after partial hepatectomy without impairing healing or liver regeneration.

The transarterial infusion of anticancer drugs is often used for irresectable liver metastases. Unfortunately, this approach is rarely successful. Partial hepatectomy, however, has been shown to prolong the survival of patients with resectable liver metastases from colonic cancer[1–4]. Patients who undergo curative resection of a solitary colorectal metastasis have a 20–38 per cent 5-year survival rate[1–3]. None the less, 61–75 per cent of patients who undergo a 'curative' liver resection of a colorectal cancer metastasis develop a recurrence in the liver within 5 years of hepatectomy. Of these patients, 36 per cent develop a recurrence within 1 year of the hepatectomy[1,2].

Patients are often encountered who have a hepatic recurrence soon after hepatectomy, suggesting that the procedure itself might stimulate tumour growth[5,6]. The mechanisms for this are not clearly defined, but several possibilities have been suggested. For example, hepatocyte growth factor, which is released in order to stimulate liver regeneration, may also serve as a tumour growth factor[7,8]. It is also possible that surgical manipulation causes tumour cell implantation in the residual liver, or that the hepatectomy and transfusion cause immunosuppression. Thus, the prevention of recurrence in the residual liver after hepatectomy may improve the prognosis of patients with resectable liver metastases.

There have been several clinical studies of adjuvant regional chemotherapy for the residual liver after partial hepatectomy for resectable liver metastases[9]. However, the results of these studies have not been wholly satisfactory[3,9]. The reasons for this failure include the possibility that the initial tumours were not sensitive to currently available drugs, and the fact that several of the agents tested had severe toxicity which discouraged their use in an adjuvant setting[3,9,10].

On the other hand, as angiogenesis is essential for the proliferation of cancer cells, the inhibition of new blood vessel growth may be a useful way to prevent liver metastasis[11]. In addition, endothelial cells do not proliferate in adults, except in a few areas of the genital organs[12]. Therefore, if endothelial proliferation could be inhibited selectively, tumour growth might be suppressed. TNP-470, a new synthetic analogue of fumagillin isolated from *Aspergillus fumigatus*, is known to inhibit angiogenesis by inhibiting DNA synthesis selectively in endothelial cells. It is also known to have an antitumour effect[11–14].

The authors have already reported that continuous infusion of TNP-470 into the hepatic artery blocks liver metastasis more effectively than injections into the jugular or portal vein[15]. Thus, TNP-470 may be able to prevent tumour recurrence in the liver after partial hepatectomy. However, it is also possible that TNP-470 may inhibit liver regeneration and wound healing because of its suppression of angiogenesis. The purpose of this study was to investigate the efficacy of TNP-470 in preventing the development of liver metastasis after partial hepatectomy, and to determine whether TNP-470 inhibits liver regeneration and wound healing, using a rabbit model.

Materials and methods

Angiogenesis inhibiting agent

TNP-470 (*O*-(chloroacetyl-carbonyl)fumagillol) was obtained from Takeda Chemical Industries, Osaka, Japan. It was mixed with cyclodextrin to increase its solubility and stability in water.

Animals and tumour cells

Twenty-four Japanese white rabbits weighing 2·4–2·8 kg were used for the study. The experimental protocols followed the 'Guidelines for the Welfare of Animals in Cancer Research' established by the Committee of Kyoto Prefectural University of Medicine.

The carcinoma cells were maintained in rabbits under endotoxin-free conditions. The VX2 tumours were broken into fine pieces, filtered through a stainless steel mesh, and suspended

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Paper accepted 7 January 1996

in Hank's balanced salt solution (HBSS) (Handai Biken, Osaka, Japan). The viability of the VX2 cells was confirmed by trypan blue staining.

Experimental procedure

The rabbits were anaesthetized with intravenous pentobarbital sodium 30 mg/kg. A laparotomy was performed through a midline incision. VX2 carcinoma cells ($1 \cdot 0 \times 10^6$)in 0·1 ml HBSS were injected into the superior mesenteric vein to produce liver metastases.

Following injection, half the rabbits underwent resection of the middle lobe of the liver (hepatectomized group), equivalent to 45 per cent of the total liver weight. The other rabbits did not undergo hepatectomy (non-hepatectomized group). The hepatectomy protocol was as follows: first, Glisson's triad into the middle lobe was ligated. The middle hepatic vein then was dissected from the liver parenchyma and ligated. The middle lobe was then removed and weighed.

TNP-470 was infused continuously for 7 days, because it has been reported that a drip infusion of TNP-470 has more efficacy and less toxicity than a bolus infusion[16]. An osmotic pump (model 2ML1; Alzet, Palo Alto, California, USA) was used for the continuous infusion of TNP-470. The pump has a 2-ml capacity and can infuse an agent at a constant rate (10 μl/h) for 7 days. Distilled water alone (2 ml) was used as a control. A polyethylene catheter, 1·22 mm in diameter (Becton Dickinson Labware, Franklin Lakee, New Jersey, USA), was connected to the pump and cannulated into the superior mesenteric vein of all animals. The treated groups (hepatectomized TNP-470-treated group, six rabbits; non-hepatectomized TNP-470-treated group, six) received 50 mg TNP-470, dissolved in 2 ml distilled water over 7 days (2·85 mg per kg per day). The control groups (hepatectomized control group, six rabbits; non-hepatectomized control group, six) received 2 ml distilled water only over 7 days. The skin and muscular layers were closed individually with a running suture of 1–0 Nurolon (Ethicon, Summerville, New Jersey, USA).

Assessment of efficacy and toxicity of TNP-470

Fourteen days after the beginning of the infusion, blood was sampled and analysed for serum glutamic–oxaloacetic transaminase (SGOT), serum glutamic–pyruvic transaminase (SGPT) and total bilirubin concentration. Thirty minutes after weighing the rabbits, 20 mg/kg 5-bromo-2′-deoxyuridine (BrdU) was infused intravenously. The rabbits then were killed and the liver was removed. The number of macroscopic tumours on the surface of each lobe of the liver was counted.

Evaluation of liver regeneration

A preliminary investigation in five rabbits indicated that the middle lobe of the liver accounted for a mean(s.e.m.) of 45(3) per cent of the weight of the entire liver. Therefore, the weight of the whole liver at the time of the partial hepatectomy (A) could be estimated as A = weight of the middle lobe/0·45.

The residual liver (B) was weighed 14 days after the partial hepatectomy. The liver regeneration ratio was defined as B/A.

For evaluating regeneration of the liver, the BrdU labelling index was calculated after staining with the avidin–biotin–peroxidase technique, with an anti-BrdU antibody. The livers of animals in the hepatectomized control and TNP-470-treated groups were fixed in 10 per cent formalin. Sections of 4 μm from each sample were dewaxed and stained with a monoclonal mouse anti-BrdU antibody (DAKO, Glostrup, Denmark) for 3 h. All endogenous peroxidase activity in the samples was blocked by incubation with 0·6 per cent hydrogen peroxide in methanol for 30 min. The samples were then incubated with a biotinylated anti-mouse immunoglobulin G (Vector Laboratories, Burlingame, California, USA) for 30 min, followed by staining with the avidin–biotin–peroxidase complex for 1 h. All incubations were performed in a moist chamber. Finally, the specimens were reacted with 3,3′-diaminobenzidine in 0·05 mol/l Tris buffer containing 0·02 per cent hydrogen peroxide for 3 min. The specimens were counterstained with haematoxylin, then dehydrated and mounted. The percentage of BrdU-positive nuclei in at least 1000 cells was determined for each specimen.

Evaluation of skin healing

To evaluate skin healing, blood flow in the incised skin was measured with a PeriFlux laser Doppler blood flow meter (Perimed, Stockholm, Sweden) and the tensile strength of the wound was determined with a spring tension meter.

The probe of the PeriFlux was placed on the skin incision of the anaesthetized animals and the blood flow was measured. All Nurolon sutures were removed, and the spring tension meter was attached 2 cm away from the wound. The wound was then stretched vertically about the site of the incision. After the bursting test, the blood flow in the muscular layer of the wound was determined.

Statistical analysis

All data are expressed as mean(s.e.m.). The results were analysed with Student's t test. $P \leq 0 \cdot 05$ was considered statistically significant.

Results

The mean(s.e.m.) number of tumours in the TNP-470-treated non-hepatectomized animals (12·3(5·4)) was significantly lower than that in non-hepatectomized controls (75·0(14·5)) (*Fig. 1*). In hepatectomized rabbits, the mean(s.e.m.) number of tumours in the TNP-470-treated group was also significantly lower than that in controls (23·3(12·3) *versus* 123·7(24·4) respectively.

There were significantly more metastatic liver lesions in the hepatectomized control group than in non-hepatectomized controls.

None of the TNP-470-injected animals exhibited significant weight loss compared with control rabbits. The SGOT and SGPT concentrations were no higher in TNP-470-treated animals than in controls. The total bilirubin level was not raised in any rabbit (*Table 1*).

The mean(s.e.m.) liver regeneration ratio of treated animals was 1·11(0·15) and that of the controls was 0·97(0·08), indicating that liver weight had returned to the prehepatectomy level by day 14. There was no significant difference in the mean(s.e.m.) BrdU labelling index between treated (15·5(2·5)) and control (15·2(4·1))

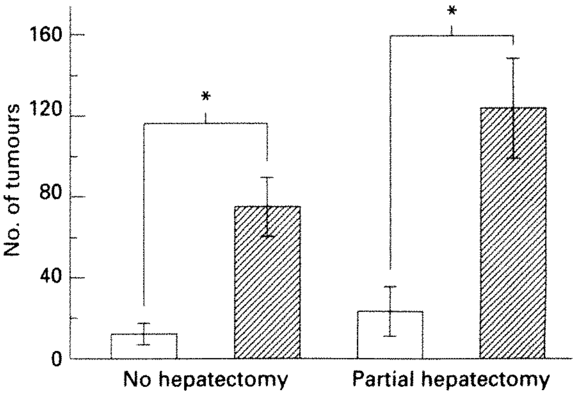

Fig. 1 Mean(s.e.m.) number of tumours in the liver of rabbits treated with TNP-470 (☐) and in controls (▨). $^*P < 0 \cdot 05$ (Student's t test)

Table 1 Effect of TNP-470 on weight loss and serum biochemistry

	Partial hepatectomy		No hepatectomy	
	TNP-470	Control	TNP-470	Control
Weight loss (g)	250(141)	91(55)	277(122)	477(42)
SGOT (units/l)	193·7(110·0)	330·5(122·5)	51·0(15·3)	73·0(29·1)
SGPT (units/l)	41·2(6·2)	99·8(27·2)	37·8(5·0)	31·2(6·9)
Serum total bilirubin (mg/dl)	0·32(0·05)	0·30(0·05)	0·25(0·04)	0·23(0·02)

Values are mean(s.e.m.). SGOT, serum glutamic–oxaloacetic transaminase; SGPT, serum glutamic–pyruvic transaminase. There were no significant differences between any of the groups

animals. Furthermore, no histological evidence of degeneration and/or necrosis was seen in the liver remnant of treated rabbits.

There was no significant difference in the mean(s.e.m.) blood flow in the skin around the incision between the treated group (45·3(13·8) units per mm^2) and the control group (42·5(14·9) units per mm^2). There also was no significant difference in the blood flow of the muscle layer between treated and control animals (41·0(12·3) *versus* 49·0(8·9) units per mm^2 respectively). A wound infection occurred in one rabbit in both treated and control groups.

The mean(s.e.m.) tension against wound bursting in the treated group did not differ significantly from that in controls (656(96) *versus* 650(134) g respectively).

Discussion

As reported by Panis *et al.*[6], partial hepatectomy accelerated the growth of liver metastases in the present study. The present authors have already reported that intra-arterial injection of TNP-470 prevents the proliferation of occult liver metastases[15]; thus, TNP-470 was expected to prevent the development of tumours in the liver remnant after partial hepatectomy. TNP-470 was injected into the portal vein, because about two-thirds of the hepatic blood is supplied from portal vein[17] and it was postulated that TNP-470 would have a greater influence on liver regeneration when administered by portal infusion. A further minor reason for intraportal injection was that cannulation at this site is technically easier than intra-arterial cannulation after hepatectomy.

Because the mean number of tumours in treated groups was significantly lower than that in untreated groups, TNP-470 infused through the portal vein may be effective in preventing growth of tumours in the liver remnant after resection of liver metastases. In the treated animals, the mean number of tumours in hepatectomized rabbits was slightly greater than that in those not undergoing hepatectomy. It is unclear whether assessing the tumour number at a later time would have made any difference.

In light of the ability of TNP-470 to inhibit angiogenesis, it was feared that it might impair liver regeneration or wound healing after operation. The side-effects of TNP-470 were evaluated using weight loss, SGOT, SGPT and total bilirubin concentrations as parameters. None of the TNP-470-injected groups suffered significant weight loss or liver dysfunction compared with controls. Therefore, the continuous intraportal administration of TNP-470 appears to have no severe adverse effects. Liver regeneration in TNP-470-injected animals was nearly complete by 14 days after hepatectomy, and was similar to that in untreated rabbits.

Why was tumour growth prevented, while liver regeneration was not impaired? Tumour cells implant primarily in the sinusoids, then migrate away and proliferate at some distance away from the vessels[18,19]. These cells need capillaries to supply nutrients and oxygen to support their growth. In contrast, hepatocytes are present along the sinusoids and can easily obtain oxygen and nutrition for proliferation. Furthermore, the endothelial cells of the sinusoidal capillaries have many intercellular and intracellular fenestrae. The sinusoidal capillaries vary in diameter and shape, and their anatomical flexibility is thought to be quite high[20]. Thus it is likely that hepatocytes can regenerate without the need for extensive proliferation of endothelial cells.

At first, it was postulated that the reason for there being no difference in wound healing between TNP-470-infused and control animals was that TNP-470 was injected into the portal vein. The metabolism of TNP-470 is not yet clearly defined, but if it occurs primarily in the liver, liver tumours may be exposed to fairly high concentrations of TNP-470 while the abdominal wall may be exposed to only low concentrations. However, in a previous experiment, intravenous and intraportal injection of TNP-470 yielded a similar efficacy in preventing liver metastasis[15], suggesting that this hypothesis is unlikely to be correct.

The abdominal wall was not examined for healing continuously after operation, but only on day 14 after surgery. Therefore, it is possible that angiogenesis and healing of the abdominal wound in TNP-470-injected rabbits might have lagged behind that of the control group during the first 7 days of TNP-470 infusion and then caught up with controls. If this hypothesis is correct, the number of induced capillaries needed to heal an abdominal wound may be less than that needed to nourish liver metastases. None the less, it is important to note that wound healing in TNP-470-treated animals was not inferior to that in controls by day 14. Thus, this study suggests that TNP-470 could be used in patients after operation, at least under certain conditions. The authors believe that TNP-470 can suppress the recurrence of liver metastasis after partial hepatectomy.

Acknowledgements

The authors thank Dr H. Okada and the Drug Delivery System Research Laboratories of Takeda Chemical Industries for supplying TNP-470, and Dr Okada for valuable comments on the study.

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British Journal of Surgery 1996, **83**, 1448–1451

Cardiac complications after hepatic resection

K. YANAGA, K. TAKENAKA, K. YAMAMOTO, T. NISHIZAKI, K. SHIRABE, M. SHIMADA, N. KAWAHARA, A. CHISHAKI* and K. SUGIMACHI

*Departments of Surgery II and *Cardiology, Kyushu University Faculty of Medicine, Fukuoka 812-82, Japan*
Correspondence to: Dr K. Yanaga

During a period of 94 months between 1985 and 1993, 474 hepatic resections were performed in 451 patients, of whom 23 (5 per cent) had cardiac problems: ischaemic heart disease in 16 (previous myocardial infarction in five and angina pectoris in 11), arrhythmic disorders in three, valvular disease in three (previous mitral valve replacement in two) and hypertrophic cardiomyopathy in one. The cardiac patients had a higher incidence of cardiac complications (24 *versus* 0 per cent, $P<0{\cdot}0001$) including two myocardial infarctions, and of non-cardiac complications consisting of postoperative liver failure (16 *versus* 4 per cent, $P<0{\cdot}01$) and bile leak (16 *versus* 5 per cent, $P=0{\cdot}02$), as well as hospital death (16 *versus* 3 per cent, $P<0{\cdot}001$). However, long-term survival was similar in the two groups. Patients with preoperative cardiac conditions appear to be at increased risk for early postoperative morbidity and mortality after hepatic resection.

With refinements in the assessment of hepatic functional reserve, surgical techniques and postoperative care, elective hepatic resection is now regarded as a safe surgical procedure[1–5]. However, being a major surgical procedure of the upper abdomen with significant intraoperative blood loss and occasional interruption of splanchnic circulation, hepatic resection could be associated with a high rate of perioperative cardiac morbidity and mortality. Although cardiac risk factors for patients who undergo non-cardiac surgery in general have been established, little is known about the significance of concomitant cardiac conditions such as ischaemic heart disease on the outcome of resection of the liver[6,7]. The purpose of this study was to clarify the effect of preoperative cardiac conditions on the outcome of elective hepatic resection.

Patients and methods

During a period of 94 months from 1 April 1985 to 18 February 1993, 474 hepatic resections were performed in 451 patients in the authors' institution. Patients' ages ranged from 15 to 79 years with a mean(s.d.) of 58·5(9·6) years; 347 (77 per cent) were men. The hepatic resection was right or left trisegmentectomy in 30 patients, bisegmentectomy consisting of right or left lobectomy as well as central bisegmentectomy in 120, resection of one segment in 75, and subsegmentectomy or less in 249. Of the 451 patients, 23 (5 per cent) who underwent 25 hepatic resections had cardiac problems: ischaemic heart disease in 16 (myocardial infarction in five and angina pectoris in 11), arrhythmic disorders in three, valvular disease in three, and hypertrophic non-obstructive cardiomyopathy in one. A patient with sick sinus syndrome underwent three hepatic resections; two of the three patients with valvular disease had had mitral valve replacement. All cardiac patients with cardiac conditions were over 50 years of age and were assigned as New York Heart Association class I.

Of the 23 patients with cardiac disease, the condition was known at the time of referral in 15 cases and was an incidental finding during preoperative investigation for abnormal electrocardiographic (ECG) findings in eight. All but two patients with ischaemic heart disease were heavy smokers.

For patients with preoperative cardiac problems, a cardiology consultation was obtained routinely. Generally, cardiac investigation for patients suspected to have ischaemic heart disease consisted of stress ECG monitoring, dipyridamole–thallium myocardial scintigraphy and echocardiography. For patients with either anteroseptal or diffuse ischaemia, coronary arteriograms were obtained to assess the extent of atherosclerosis. For patients with valvular heart disease, echocardiography was performed to assess left ventricular function.

Regular perioperative care for patients who underwent hepatic resection included fluid restriction with 30–40 ml kg^{-1} of intravenous fluid containing 5–10 per cent dextrose per day. For patients with hepatic dysfunction, sodium intake was strictly limited. For cirrhotic patients, spironolactone 200 mg was administered intravenously during the early postoperative period. For hypoalbuminaemia, 25 g salt-poor albumin was infused intravenously. Central venous pressure was measured as needed. For urine output of less than 0·5 ml kg^{-1} h^{-1} with hypovolaemia, plasma protein fraction or salt-poor albumin was infused as assessed on an hourly basis, while low urine output with an adequate intravascular volume was treated by intravenous frusemide. The nasogastric tube was removed on the first postoperative day, and oral intake was started the next day.

Pulmonary artery pressure was monitored by a Swan-Ganz catheter in six of the 23 cardiac patients: four who had had a previous myocardial infarction, one with hypertrophic non-obstructive cardiomyopathy and one after mitral valve replacement. After operation seven patients stayed in the intensive care unit for 1–9 (mean 2) days. Patients with ischaemic heart disease were given nitroglycerin intravenously or as a paste patch.

For the two patients who had had mitral valve replacement, perioperative anticoagulation coverage was with heparin, which was converted back to warfarin as soon as oral intake was resumed.

A patient with an atrioventricular pacemaker for sick sinus syndrome underwent three hepatic resections with fixation of the pacing rate during the procedure.

The perioperative details of patients with cardiac disease were compared with those of the other 428 with no preoperative cardiac disease who underwent 449 hepatic resections during the same period. Intraoperative hypotension was defined as systolic blood pressure below 80 mmHg for more than 10 min.

Statistical analysis was with the two-tailed Student's t test or the χ^2 test for data comparison; survival was analysed with the Kaplan–Meier method. Results are expressed as mean(s.d.). $P<0{\cdot}05$ was considered statistically significant.

Paper accepted 7 January 1996

Results

The annual incidence of hepatic resection for patients with preoperative cardiac conditions has been 14 (10 per cent) of 147 patients since 1992, which was significantly higher than 11 (3 per cent) of 328 before 1992 ($P < 0\cdot01$).

Patients aged 50 years or older had a significantly higher incidence of cardiac conditions compared with younger patients (25 (6 per cent) of 402 *versus* 0 of 72, $P = 0\cdot04$).

There was a higher incidence of diabetes mellitus (11 (44 per cent) of 25 *versus* 81 (18 per cent) of 449, $P < 0\cdot01$) and hypertension (13 (52 per cent) of 25 *versus* 73 (16 per cent) of 449) among patients with cardiac conditions, while other data including liver function were similar in the two groups.

Table 1 compares intraoperative data between patients with and without preoperative cardiac conditions. All variables evaluated were similar in the two groups.

Table 2 shows morbidity and mortality after hepatic resection in patients with and without preoperative cardiac conditions. The incidence of cardiac complications was significantly higher in patients with preoperative cardiac conditions than in those without. Two patients who had had a previous myocardial infarction had a postoperative infarction. Of the two patients who developed acute myocardial infarction after hepatectomy, rapid expansion of the tumour was judged to preclude preoperative coronary artery bypass surgery for three-vessel disease in one case. In the other patient, exercise ECG findings were negative, and follow-up coronary angiography with possible percutaneous transluminal coronary angioplasty (PTCA) was deemed unnecessary. One patient, 71 days after myocardial infarction and treatment with PTCA, underwent hepatic resection without recurrent infarction. Clinically significant arrhythmias occurred in two patients in each group: atrial fibrillation with tachycardia and frequent ventricular premature contractions in those with a previous cardiac condition, and atrial fibrillation with tachycardia and supraventricular tachycardia in those without.

Contrary to the marked difference in cardiac complications, the overall incidence of non-cardiac complications was similar in the two groups. Neither of the two patients anticoagulated by heparin for replaced mitral valves developed haemorrhagic complications. Liver failure and bile leaks were more frequent in those with preoperative cardiac conditions. The incidence of hospital death was markedly different between the two groups, due primarily to the higher incidence of liver failure in patients with preoperative cardiac conditions.

Table 1 Comparison of intraoperative and postoperative data in patients with and without preoperative cardiac conditions

	Preoperative cardiac condition	
	Yes ($n = 25$)	No ($n = 449$)
Operating time (min)*	286·3(85·4)	285·8(120·0)
Blood loss (ml)*	1614(1065)	1877(2455)
Blood transfused (ml)*	864(919)	888(1951)
Extent of resection†	2/9/4/10	28/111/71/239
Resection volume (g)*	380(295)	326(417)
Tumour diameter (cm)*	5·0(3·8)	4·3(3·4)
Intraoperative hypotension‡	3 (12)	80 (18)
Postoperative haematocrit (%)*§	10·0(1·6)	10·7(8·5)

*Values are mean(s.d.); †trisegmentectomy/bisegmentectomy/segmentectomy/subsegmentectomy or less; ‡values in parentheses are percentages; §value on day 3 after operation

Table 3 lists morbidity and mortality after hepatic resection in patients with cardiac conditions. All hospital deaths were in those with ischaemic heart disease for whom the hospital death rate was four of 16 patients in spite of average incidence of postoperative complications.

Of the five patients with a previous myocardial infarction who underwent hepatic resection, two did not undergo coronary angiography before operation but did well after surgery. Another patient had undergone uncomplicated abdominal aortic aneurysmectomy and Hartmann's procedure for cancer of the sigmoid colon 13 months before hepatectomy at another hospital. After right hepatic lobectomy for liver metastasis, this patient developed intra-abdominal bleeding and required laparotomy for haemostasis. After the reoperation he developed liver failure followed by autopsy-proven acute myocardial infarction and died from multiple organ failure. Another patient had undergone PTCA after suffering from myocardial infarction 33 months before

Table 2 Morbidity and mortality after hepatic resection

	Preoperative cardiac condition		
	Yes ($n = 25$)	No ($n = 449$)	P*
Cardiac complications	6 (24)	2 (0)	< 0·0001
Acute myocardial infarction	2 (8)	0 (0)	< 0·0001
Angina pectoris	2 (8)	0 (0)	< 0·0001
Arrhythmia	2 (8)	2 (0)	< 0·0001
Non-cardiac complications	11 (44)	219 (49)	0·49
Liver failure	4 (16)	18 (4)	< 0·01
Subphrenic abscess	3 (12)	37 (8)	0·51
Bile leak	4 (16)	23 (5)	0·02
Postoperative bleeding	1 (4)	14 (3)	0·81
Ascites	4 (16)	70 (16)	0·96
Pleural effusion	4 (16)	104 (23)	0·41
Hospital death	4 (16)	13 (3)	< 0·001

Values in parentheses are percentages. *χ^2 test

Table 3 Morbidity and mortality after 25 hepatic resections in 23 patients with cardiac conditions

	Complications			
Cardiac disease	Cardiac	Non-cardiac	Overall	Hospital death
Ischaemic heart disease ($n = 16$)	5*	7	8	4†
Arrhythmias ($n = 5$)	1	4	4	0
Valvular disease ($n = 3$)	0	1	1	0
Cardiomyopathy ($n = 1$)	0	0	0	0
Overall	6	12	13	4

*Includes one patient who developed acute myocardial infarction 22 days after discharge; †liver failure in three patients and bile peritonitis in one

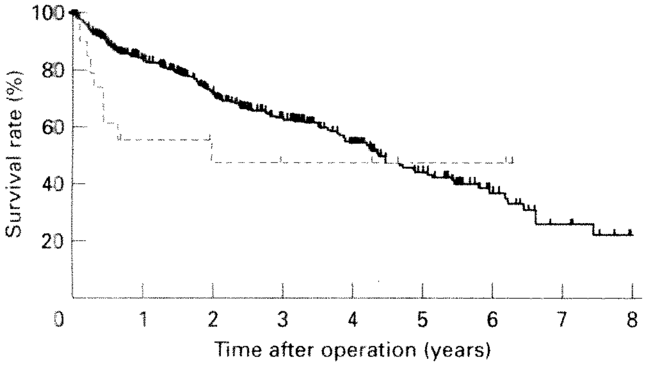

Fig. 1 Patient survival after hepatic resection. Patients with a preoperative cardiac condition (– – – –) showed a sharp decline in survival for the first 6 months after operation. Thereafter, survival was similar to that in patients with no preoperative cardiac problems (———). Overall there was no significant difference between the two groups

hepatic resection. Investigation by double master electrocardiography and stress thallium myocardial scintigraphy showed no abnormality and coronary angiography was not performed. This patient underwent right trisegmentectomy for a rapidly growing primary malignant lymphoma. He was discharged 20 days after operation but developed acute myocardial infarction 22 days later, for which PTCA was again performed. He remains alive and well. The other patient with cholangiocarcinoma was operated 71 days after myocardial infarction. Because of rapid growth of the cancer, right hepatic lobectomy was performed immediately after successful PTCA of the right coronary artery to reduce stenosis from 99 to 25 per cent, and the patient's postoperative recovery was uneventful.

Fig. 1 shows the survival of the patients with and without cardiac conditions after hepatic resection. Although the short-term survival of cardiac patients was not as good as that of non-cardiac patients, the long-term survival rate was similar in the two groups.

Discussion

Cardiac conditions known to be associated with circulatory complications after non-cardiac surgical procedures include ischaemic heart disease, preoperative arrhythmias or heart failure, aortic valvular disease and hypertrophic obstructive cardiomyopathy. Of these, previous myocardial infarction within 6 months and present congestive heart failure are regarded as the most dangerous[6,7]. Non-cardiac risk factors for cardiac complications after non-cardiac operations include age over 70 years, emergency surgery, major vascular surgery, and prolonged thoracic or upper abdominal surgery[6,7].

Measures to reduce cardiac complications include accurate assessment of cardiac conditions by various diagnostic techniques, correction of circulatory problems including preoperative control of congestive heart failure or correction of significant coronary artery stenosis by bypass surgery or PTCA before contemplated surgery and intraoperative haemodynamic monitoring with an arterial line and a pulmonary artery catheter[6–10].

As to the relevance of concomitant cardiac conditions to the outcome of hepatic resection, Stimpson *et al.*[1] in 1987 described their experience with 58 elective major hepatic resections; ECG findings were not a sensitive indicator of postoperative cardiac complications. Iwatsuki and Starzl[2] in 1988 reported that two of 411 patients developed acute myocardial infarction, of whom one died during operation. Belghiti *et al.*[10] in 1993 documented 81 patients who underwent elective hepatic resection, of whom one (1 per cent) died from a myocardial infarction that occurred 24 h after surgery. Of 90 patients aged at least 65 years who underwent elective hepatic resection, Fortner and Lincer[3] reported postoperative cardiac complications in 11 (12 per cent), consisting of arrhythmias in five (6 per cent), congestive heart failure in four (4 per cent) and acute myocardial infarction in two (2 per cent). Of two patients with postoperative myocardial infarction, one had had a previous infarction and required an emergency operation for haemobilia, and the other with a normal preoperative electrocardiogram developed a fatal infarction 12 h after surgery; autopsy revealed 90 per cent stenosis of four cardiac vessels.

For cardiac patients with malignancy, tumour growth and spread need to be weighed against the time required for cardiac investigation and correction of cardiac problems. As to the safety of non-cardiac surgical procedures after coronary revascularization procedures, Mahar *et al.*[11] reported no perioperative myocardial infarction among 99 cardiac patients who underwent 168 operations following coronary artery bypass. Crawford *et al.*[12] also demonstrated that the operative risk of patients with previous coronary artery bypass is similar to that of patients with no coronary artery disease.

Although the present authors' experience with myocardial revascularization procedures is limited, such preparations for elective hepatic resection seem important to reduce postoperative myocardial infarction among high-risk candidates[9,11,12]. Although PTCA is less invasive than coronary artery bypass, early restenosis is common: 13 per cent within 1 month and 43 per cent within 3 months in one study[13]. Therefore, we consider that coronary angiography is necessary for cardiac evaluation if PTCA has been performed more than 3 months before the prehepatectomy investigations.

The high incidence of liver failure and bile leak after elective hepatic resection for patients with concomitant cardiac conditions in the present series is noteworthy. Liver failure among cardiac patients could be attributed to postoperative intra-abdominal bleeding in one and to bile peritonitis in another, and possible excessive resection in a 70-year-old woman with hepatic cirrhosis, while the cause was undetermined in the other patient who had been on haemodialysis for chronic renal failure. To reduce early postoperative mortality and morbidity after hepatic resection, patients with cardiac conditions should undergo hepatectomy with special attention to minimizing intraoperative blood loss and haemodynamic instability, and to achieving perfect haemostasis and control of bile leaks from the raw liver surface. For cardiac patients with concomitant liver cirrhosis, non-cancerous hepatic parenchyma should be preserved as much as possible[14].

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British Journal of Surgery 1996, **83**, 1452–1455

Pilonidal sinus: experience with the Karydakis flap

P. R. B. KITCHEN

Department of Surgery, St Vincent's Hospital, 41 Victoria Parade, Melbourne, Victoria 3065, Australia
Correspondence to: Mr P. R. B. Kitchen

A personal series of 141 patients with postanal pilonidal sinus was treated by the Karydakis operation. Each sinus was totally excised with a vertical eccentric elliptical excision. A thick flap was created by undercutting the medial edge and advancing it across the midline so that the whole suture line was lateralized to reduce the risk of recurrence. Follow-up was achieved in 114 patients for 1–108 months; 79 (69 per cent) were followed for more than 18 months. Overall there were five recurrences (4 per cent) which required further surgery. Thirty-three patients (23 per cent) were referred following recurrence or failure of healing after previous surgery elsewhere; all were cured by this method. The Karydakis operation has a low recurrence rate because it produces a shallow midline furrow free from scar or suture holes which is less vulnerable to hair penetration than a midline wound.

Pilonidal sinus may be treated in a number of ways. Karydakis[1] published the largest series in the literature (6545 cases) and argued for a technique that prevents recurrence as well as curing the presenting condition. The present author has used this method successfully since 1973, finding it to work especially well in difficult cases referred when other surgery has failed. This paper emphasizes some of the details of operative technique designed to ensure a successful outcome.

Patients and methods

The operation was performed on 141 consecutive patients with chronic postanal pilonidal sinus between December 1973 and February 1995. Details of some of these patients have been reported previously[2]. Mean age was 25 (range 13–64) years. Overall 70 per cent of patients were male and 45 per cent were of Mediterranean (Greek, Italian or Arabic) origin. Patients presented with discharge (47 per cent), a lump alone (20 per cent) and/or a history of previous abscess (53 per cent). Follow-up after operation was achieved in 114 patients (81 per cent) and involved personal contact with each or, if this was impractical, a telephone call made to the referring doctor. Median follow-up was 22 (range 1–108) months and 79 patients (69 per cent) were followed for more than 18 months.

Thirty-three patients (23 per cent) presented with recurrence after previous surgery by other surgeons; seven had persistently unhealed midline wounds and 18 had had previous surgery on two, three or four occasions. All sites of previous recurrence were in the midline. Four patients had inadequately lateralized scars from a previous Karydakis operation in which sinuses recurred where the scar met the midline, and three had failed Z-plasties, with openings at the lower end of the scar. One patient with an unhealed wound had a new sinus extending into the anus.

Surgical technique

An asymmetrical biconcave ('elliptical') incision is made, with the patient positioned prone and with the buttocks strapped apart. The ellipse is based on the side of any secondary opening or induration; if the sinus is entirely central, either side may be chosen. The incision is at least 5 cm long with gentle curvature. Each end of the incision is placed 2 cm to one side of the midline (*Fig. 1*). The medial edge of the excision crosses the

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Paper accepted 21 November 1995

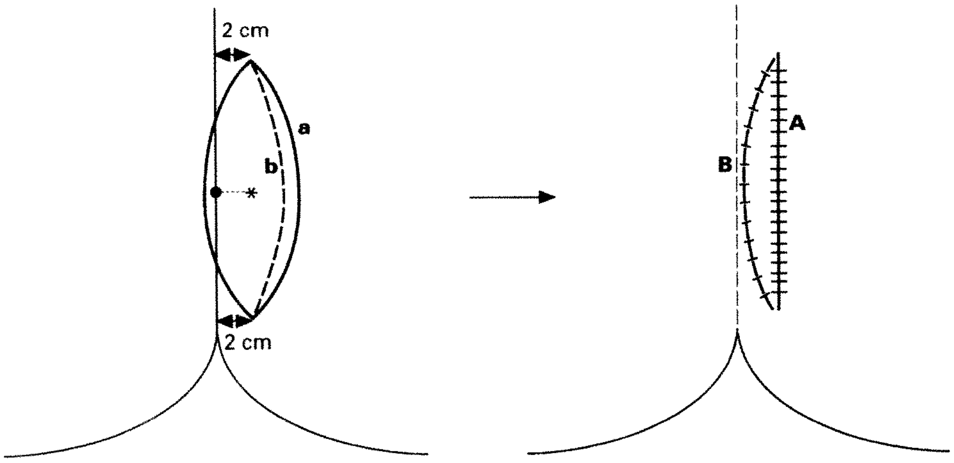

Fig. 1 Left: a biconcave incision started and centred 2 cm to one side of the midline cleft and skirting the cleft just sufficiently to excise the primary opening (●) and whole track. If there is a secondary opening (*) it may be the centre of this ellipse. If the sinus is entirely in the midline the centre could be on either side. The lateral edge (**a**) must be cut symmetrically with the medial edge. If less is excised laterally to conserve tissue (**b**) a wound will be produced (right) that tends to lie in the midline (**B**) with a higher risk of recurrence than a well lateralized wound (**A**)

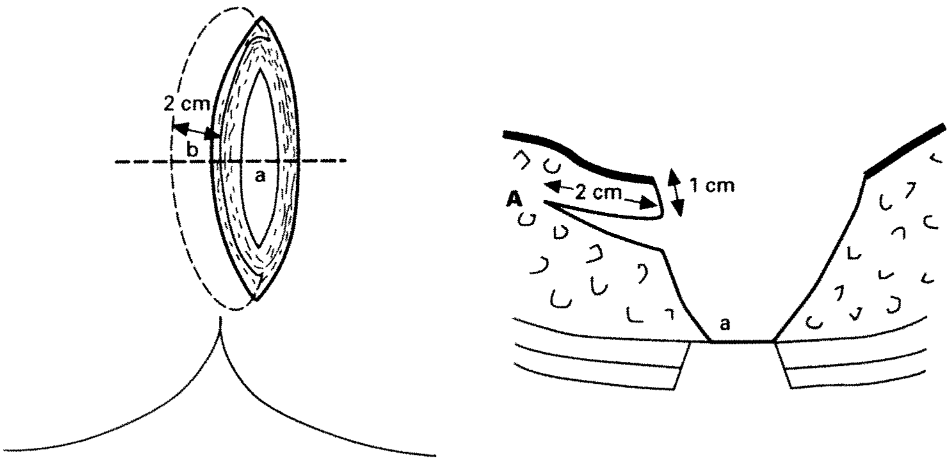

Fig. 2 On the right is a cross-section of the centre of the wound indicated on the left with a dashed line. A wedge of tissue is excised including the full sinus track down to the sacral fascia (**a**) and a lateral flap is created along the full length of the medial edge, undercutting a distance of 2 cm at a depth of 1 cm

midline sufficiently to encompass the primary pit. Probing and insertion of povidone–iodine or methylene blue helps to ascertain the extent of the sinus so that the whole sinus and its ramifications can be fully excised without inadvertent contamination of the wound by opening the track. The lateral edge of the excised ellipse must be symmetrical with the medial edge even if this means excising more skin and fat well beyond the sinus, so that the final suture line is vertical, or its central part may encroach towards the midline, which increases the risk of recurrence. The scalpel is inserted down to muscle and sacral fascia to remove a boat-shaped wedge of tissue including the whole sinus. Diathermy is not used until the tissue has been excised to avoid confusion of burn marks with methylene blue from divided sinus branches. The medial side of the wound is then undercut a distance of 2 cm at a depth of about 1 cm to produce a flap extending the full length of the wound (*Fig. 2*). The flap should be of uniform thickness. Cutting the flap may expose the deep fascia and muscle in a thin patient but will be within fat in obese patients.

A layer of interrupted absorbable sutures (1 chromic catgut or dexon) is placed before any is tied, the needle being passed into the sacral fascia in the midline and then deeply into the fat at the base of the flap, taking a large bite that includes both surfaces of the undercut (*Fig. 2, point A*). As this series of sutures is tied, the assistant can both evert the edge with fingers and use a thumb to push the base of the flap across to the midline to approximate the surfaces for knotting (*Fig. 3*). A suction drain is placed across these knots and brought out well laterally before the second layer of sutures is placed to approximate the undersurface of the flap to the fat in the lateral edge of the wound. During insertion of these sutures the assistant can evert the edge and hold knots during tying as before. A useful modification is to take an additional bite of deeper fat or fascia while placing these sutures, which helps flatten the flap and avoids a dead space (*Fig. 4*). Interrupted fine nylon sutures are placed in the skin. If the skin edge on the flap tends to invert, a further shallow cut can be made just beneath the skin of this edge to evert it and vertical mattress manner knots used where necessary. These should not be tied tightly to avoid necrosis of the skin edge. Care should be taken to leave no suture hole, drain hole or any part of the wound in the midline.

In the unusual situation where there are secondary openings on both sides of the midline, a small side-cut into the wound edge may be necessary to fully excise the track extension and opening. The wound then has a T-junction which is closed with an apical skin suture (*Fig. 5*).

One dose of intravenous antibiotic is given during the operation and a firm dressing is applied to the closed wound. A rolled pad can be used over gauze to flatten the flap and help create a new shallow midline furrow. The patient is nursed supine in the recovery room to help haemostasis by pressure. The patient is kept in bed for 2 days, to prevent haematoma formation; after this period the drain is removed and the dressing is replaced before discharge from hospital on the third

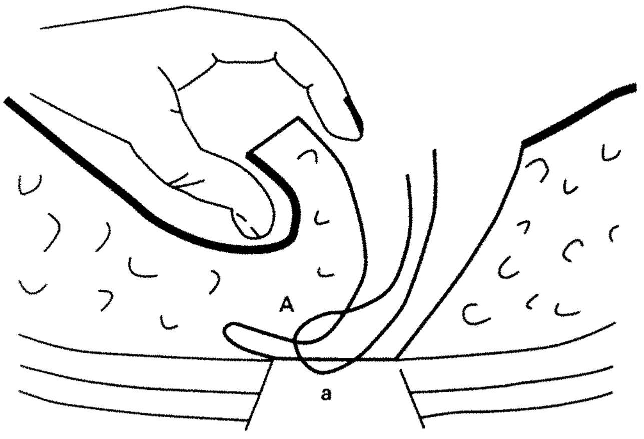

Fig. 3 The deepest sutures are all placed before any is tied, the assistant pushing the base of the flap across and everting its edge to aid tying of the knot (**A** to **a**)

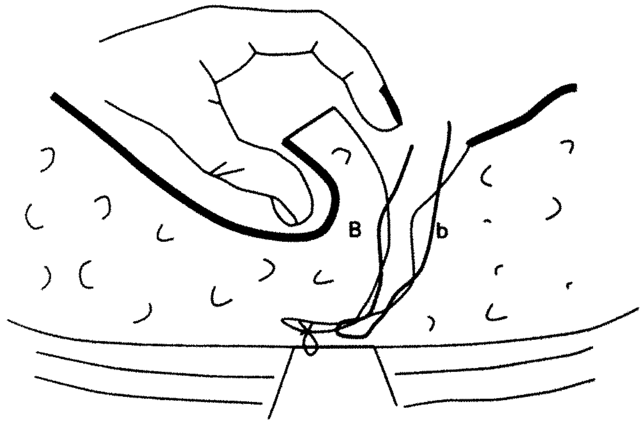

Fig. 4 The second layer of absorbable sutures apposes two surfaces (**B** to **b**) and also takes a deeper bite to avoid a dead space

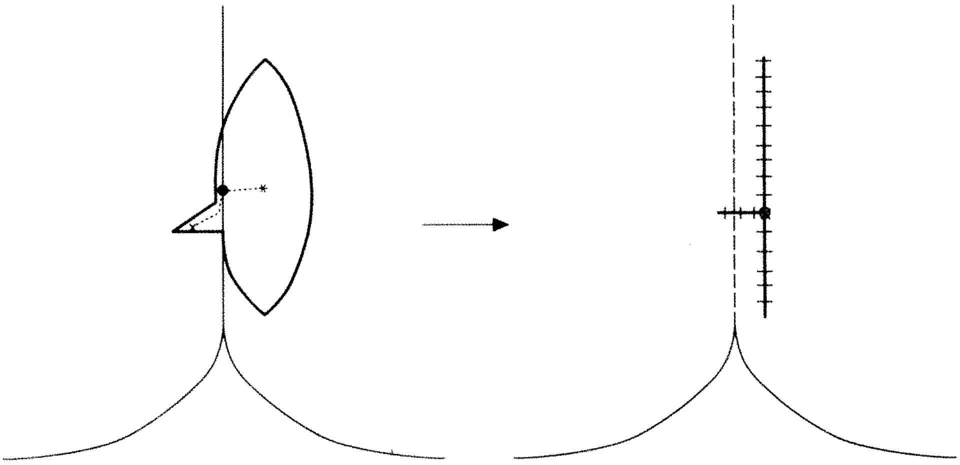

Fig. 5 When there are secondary openings on both sides, the most lateral or larger is chosen as the centre for the elliptical excision. Once the sinus is excised, a V cut is made into the other edge to excise the track and opening fully (left). The edges of this V are sewn together and brought across to the opposite surface with an apical suture to form a T-junction (right)

or fourth day. Sutures are removed after 10 days. Patients return to work in the third or fourth week. It is wise to shave the wound and around it twice weekly for a month, but this can then cease.

Results

Mean length of hospital stay was 4 days and most patients returned to work within 4 weeks. Immediate postoperative complications were haematoma in seven patients and wound infection in six. Late complications were some wound numbness in 17 patients (12 per cent) and slow healing in four (3 per cent). There were five known recurrences (4 per cent) from 9 to 18 months after operation; all were in the midline. Four recurrences occurred in the first half of the series in cases where the wound encroached on to the midline. One was a new sinus in the new midline furrow. They were cured by curettage (two patients), laying open (one) or a second Karydakis procedure (two). All 33 patients who presented with recurrence (26) or failure of healing (seven) after previous surgery were dealt with successfully by the Karydakis method. Some of these required large eccentric excisions producing well lateralized wounds. Only one of these has developed a further recurrence which was small and was cured by curettage.

Discussion

A major cause of pilonidal sinus is insertion of loose hairs that collect in the gluteal furrow. This tendency is aggravated in individuals with a deep cleft or a portal for hair entry in the midline[3]. Good postoperative advice is to rub the furrow daily with a rough towel after bathing to remove loose hairs, but indefinite shaving of the buttocks or use of depilatory creams will only set up irritation and is unnecessary since the cause of the sinus is gathered loose hairs entering by their roots[2], not hairs growing in the buttock skin[4]. Most operations can cure the sinus but risk development of recurrence, either in the short term (failed wound healing) or long term (new sinus development[5]). Early recurrence may be due to the presence of a wound in the midline acting as a portal for hair entry, and later recurrence may occur because of a deep furrow, in which loose hairs may collect. Surgery should not only eradicate the presenting sinus but should also aim to eliminate factors that predispose to formation of another sinus. This is achieved by reducing the depth of the cleft and ensuring that all parts of the wound and all suture holes are away from the midline. Bascom's cleft closure operation[6] produces a lateral wound and the Z-plasty procedure[7] and V-Y fasciocutaneous flap[8] reduce the depth of the natal cleft and hence have low recurrence rates[9]. However in the present series there were three patients who presented with recurrence after previous Z-plasty when new sinuses occurred at the lower end in the midline where the wound meets the midline and the cleft is not flattened.

The aim in all surgery should be to minimize both the financial cost to the community (treatment efficiency) and the cost to the patient in terms of time off work, number of dressings and postoperative visits, complications and recurrences (treatment effectiveness). Allen-Mersh[9] in 1990 extensively surveyed the literature on various operations and their results. Karydakis[1] reports the largest patient numbers and has a very low recurrence rate (1 per cent) at 2 years or more. Some series have shorter follow-up, which means their recurrence rates may be underestimates[5]. Excision with an open wound involves prolonged hospitalization or clinic attendance for many painful dressings and takes months to heal. Both that method and excision with marsupialization leave a portal in the midline for further hair entry and have a small but significant recurrence rate[9-14]. Several series have shown that excision with primary closure is preferable to excision with an open wound in many respects: less bleeding, less wound breakdown, lower infection rate, reduced wound pain, fewer postoperative visits, shorter time off work and faster healing time[11,13,15]. These advantages outweigh any increase in recurrence rate.

Day surgery with simple laying open, curettage, brushing or phenol injection may get rid of the hairs and cure the sinus but the midline wound may take several weeks to heal and there is a significant recurrence rate because of the open portal for hair insertion[9]. Thus the advantages of simple day surgery may be outweighed by the longer time to return to work and the greater likelihood of a further operation with longer hospitalization for recurrence. Asymmetric excision with a Karydakis flap is the only operation that takes the whole wound away from the midline. It is easy to learn and teach, and this study confirms that it has a very low recurrence rate, fast healing time and short period off work.

Acknowledgements

The author wishes to acknowledge the work of the late Dr George Karydakis, whose extensive experience and excellent results stimulated his interest in this approach to pilonidal sinus.

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British Journal of Surgery 1996, **83**, 1456–1458

Brush cytology for the diagnosis of rectal carcinoma

R. FAROUK, J. EDWARDS*, M. THORNE, W. YOUNG*, A. W. MACDONALD, J. R. T. MONSON and P. W. R. LEE

*Academic Surgical Unit, University of Hull and *Department of Pathology, Castle Hill Hospital, Castle Road, Cottingham, Hull HU16 5JQ, UK*

Correspondence to: Professor J. R. T. Monson

The use of brush cytology as an aid in the preoperative diagnosis of rectal cancer was prospectively assessed at 328 examinations in 289 consecutive patients with rectal lesions suspicious of carcinoma. Forty-five patients were reported as having benign polyps. There was 97 per cent agreement between conventional biopsy and cytology brushings for this group. Some 249 patients underwent a subsequent resection allowing comparison with formal histology. Forceps biopsy produced a true-positive diagnosis of cancer in 218 patients (89·7 per cent) and cytology in 222 (91 per cent). The sensitivity for forceps biopsy and cytology was 81 and 83 per cent respectively, with a combined sensitivity of 98 per cent. It is concluded that the addition of cytology to forceps biopsy increases the diagnostic yield in a single examination, and may be a complementary method of establishing the diagnosis of rectal lesions.

Where there is clinical suspicion of a rectal carcinoma, it is mandatory to obtain histological diagnosis before treatment. Histological confirmation of the diagnosis is conventionally achieved by forceps biopsy. Finger-guided biopsy may be used for very low rectal lesions[1]. Forceps biopsy is occasionally difficult because of the anatomical site of the tumour, or because the tumour is obscured by bowel content or blood-stained mucus, or both. Occasionally, the lesion encountered is widespread, raising the difficulty of perhaps missing a malignant area in a very large adenoma. Apart from the complications of perforation and haemorrhage, biopsy may be inconclusive because of unsatisfactory samples. The patient's management is therefore delayed while re-examination for further biopsy specimens is undertaken. The use of brush cytology in the diagnosis of colorectal malignancy and to determine the aetiology of colonic strictures has previously been demonstrated to be feasible[2–6]. The aim of this study was to assess brush cytology as an aid for the diagnosis of rectal cancer.

Patients and methods

A total of 289 consecutive patients seen at a rectal outpatient clinic, over a 3-year period, with rectal lesions suspicious of carcinoma were studied prospectively. Each patient underwent a full anorectal examination, and the lesion was then brush biopsied with a Cytotec (Cell Path, Hemel Hempstead, UK) cervical smear brush. The brush was rubbed and turned against the lesion directly, or via a sigmoidoscope. The brush head was then placed in cytological fixative solution and transported to the pathology laboratory where the cytologist prepared the slides. A conventional forceps biopsy of the lesion was then performed. If the latter biopsy yielded a negative result, the patient was re-examined, and repeat brushings and biopsy specimens were obtained. Some 249 patients subsequently underwent surgical resection, allowing the final diagnosis to be established by means of histological examination of the resected specimen.

Results

The results obtained by forceps biopsy were reported as either positive or negative for carcinoma. Cytological interpretations of the brushings were expressed as positive for (grade C5), or suspicious of (C4), carcinoma, benign

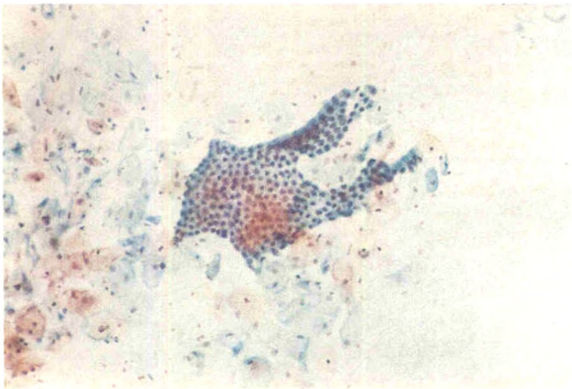

Fig. 1 Malignant cells on brush cytology. Note the large pleomorphic nuclei, with minimal clumping of cells. (Haematoxylin and eosin stain, magnification ×25)

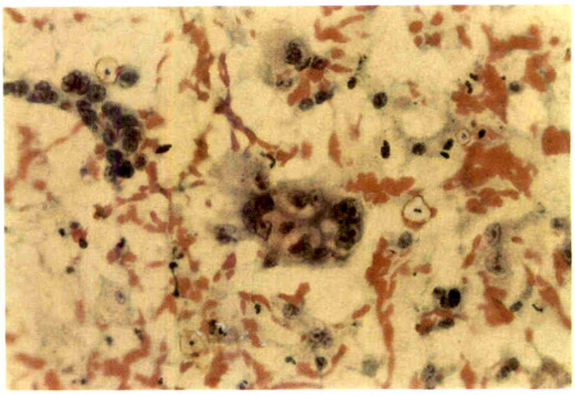

Fig. 2 Example of a brushing from a benign rectal polyp. The nuclei are uniformly small, and cell cohesion is observed. (Haematoxylin and eosin stain, magnification ×10)

Presented to the Association of Coloproctologists of Great Britain and Ireland in Cork, Ireland, July 1995
Paper accepted 10 December 1995

Table 1 Summary comparing results from forceps biopsy and cytology brushings for the diagnosis of rectal carcinoma

	Forceps biopsy	Cytology brushings
True positive (*n* = 244)	215 (88·1)	221 (90·6)
True negative (*n* = 45)	45 (100)	44 (97·8)
False positive (*n* = 289)	0 (0)	1 (0·005)
False negative (*n* = 244)	34 (13·9)	23 (9·4)

Values in parentheses are percentages

(C2), or insufficient for diagnosis. Cytological diagnosis of malignancy was made on the basis of poorly cohesive cells with large, darkly staining nuclei (*Fig. 1*). Benign brushings were identified as large groups of cells showing cohesion, with normal nucleus:cytoplasm ratios (*Fig. 2*).

Thirty-nine patients (13·5 per cent) with a negative result from the initial forceps biopsy, but who had a cytology brushing report suspicious of malignancy required re-examination with further biopsy and brushing. The initial biopsy and brushings result for these patients, and not the repeat examination outcome, have been used for subsequent analysis.

Four patients had inadequate cytological brushings for reporting but had positive forceps biopsy results. Forty-one patients were found to have benign polyps, all of which were correctly identified by forceps biopsy and 40 by cytological brushings. The final histological diagnosis of the resected specimens showed that 244 of the 249 patients undergoing surgical resection had an adenocarcinoma of the rectum. Five patients had villous adenomas with a high degree of dysplasia but without carcinomatous change (*Table 1*).

A true-positive diagnosis of cancer was made by cytology in 207 patients (84·8 per cent). A further 14 patients (5·7 per cent) were regarded as suspicious for malignancy. There were 23 false-negative reports (9·4 per cent), nine of which were for 'atypical' tumours: anaplastic carcinoma of the rectum (three patients), squamous carcinoma of the rectum (one), metastatic oat-cell bronchial carcinoma (one) and squamous carcinoma of the anus encroaching upon the rectum (four).

Forceps biopsy produced 215 (88·1 per cent) reports of a true-positive carcinoma of the rectum, while there were 34 (13·9 per cent) false-negative diagnoses. There was agreement between cytology (positive and suspicious reports) and forceps biopsy on a positive result in 216 cases (88·5 per cent). The sensitivity for cytology and forceps biopsy was 83 and 81 per cent respectively, with a combined sensitivity of 98 per cent. The specificity of cytology and forceps biopsy was 90 and 100 per cent respectively.

The five patients who underwent anterior resection for a villous adenoma did so because of the high degree of dysplasia, and the extensive nature of these lesions. These five patients were correctly identified as showing no evidence of malignancy by forceps biopsy. Cytology correctly diagnosed four of these five patients as being negative for malignancy, but in the remaining patient provided a diagnosis of suspicious for malignancy.

Discussion

Cytological diagnosis of rectal cancer was first described as a case report by MacKenzie and Hechte in 1948[7]. The use of a brush for exfoliative cytological diagnosis of colorectal lesions was first advocated by Ayre and Oren[3]. The application of digital scrape cytology was subsequently described[1]. The histological confirmation of rectal cancer, however, remains mainly confined to the use of forceps biopsy via a sigmoidoscope. Such a technique allows unequivocal evidence of submucosal invasion indicative of malignancy. Cytological diagnosis is based on cell morphology and cannot give information on architectural evidence of invasion[8]. An endoscopic finding of an ulcerated or annular lesion is unlikely to be an adenomatous polyp, however, and the finding of cytologically malignant cells from the brushings of such a lesion can therefore be safely interpreted as indicative of a carcinoma.

In this report, cytology incorrectly diagnosed one of five villous adenomas that were resected to be suspicious for malignancy. This reflects previous findings that the surface of adenomas may contain dysplastic or even malignant cells without evidence of invasion[8]. While the five patients underwent subsequent resection because of the extensive nature of these polyps, it emphasizes the need for caution in the cytological interpretation of polypoid lesions. There were also 23 false-negative reports based on cytology. In nine of these patients, there was a failure of interpretation because of the atypical nature of the tumour. This contrasts with previous reports which suggest that it is a failure of the sampling process rather than a misinterpretation that results in false-negative reports[2,6]. Such false-negative sampling was also seen in 34 patients who were biopsied and not reported to have a tumour, although cytology brushings were malignant. Re-examination and biopsy confirmed the presence of tumour in these patients. The false-positive rate of cytology brushings from this series is therefore 0·3 per cent (one in 289 patients) with a false-negative rate of 9·4 per cent. These rates are favourable compared with those for cytological diagnosis of breast cancer[9,10].

The sensitivity of the cytology brushings was comparable with that of forceps biopsy (84 *versus* 81 per cent respectively). When the two methods are combined, the sensitivity improved to 98 per cent. This increase in diagnostic yield compares with that observed from smaller series. Cytology has previously been shown to have a sensitivity of 82 per cent compared with 80 per cent for forceps biopsy in a series of 130 patients with primary colorectal carcinoma[5]. The combined sensitivity of the two methods was 97 per cent in this study. In a separate study, Bemvenuti *et al.*[4] reported the results of 202 brushings, 23 of which were from carcinomas. Cytology brushings correctly identified malignancy in 18 patients (82 per cent). Among the 179 benign lesions in this series, there were no cytological false positives, with 174 reports being correct. In addition, Mortensen *et al.*[6] have described the results of colonoscopic brushings from 79 patients with strictures. Brush cytology was shown to be considerably more accurate (81 per cent) than endoscopic biopsy (61 per cent) in the diagnosis of the aetiology of colonic strictures.

At present brush cytology appears to be best suited as a complementary investigation to forceps biopsy given its limitations with polypoidal lesions, and a definite false-negative rate. It is a quick, simple and complication-free manoeuvre that can increase diagnostic yield. Brush cytology can provide important confirmation of malignancy, and may prevent the need for re-examination.

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British Journal of Surgery 1996, **83**, 1458

Surgical workshop

Subcutaneous bridge support for defunctioning loop colostomy

S. W. ATKINSON and P. G. BENTLEY

Department of Surgery, Kent and Sussex Hospital, Mount Ephraim,
Tunbridge Wells TN4 8AT, UK
Correspondence to: Mr P. G. Bentley

It is conventional to support a loop colostomy for a number of days after it has been fashioned to prevent retraction into the abdomen. This manoeuvre is usually accomplished by a plastic 'bridge' overlying the incision used to create the stoma. This technique has the disadvantage of not only preventing complete mucosa-to-skin apposition but also causing difficulties in fitting an appliance to encircle the stoma accurately. A modification of this common procedure that obviates these difficulties is described.

Surgical technique

The colon is exteriorized, and a defect for the stoma is created in the anterior abdominal wall in the standard fashion. Incisions (5 mm) are made in the skin in a transverse direction to the normal orientation of the colon, 5 cm from the stoma. A Jacques catheter or nasogastric tube is passed subcutaneously from one incision, behind the colon to be exteriorized, and again subcutaneously to exit from the other incision (*Fig. 1*). The colon is opened and sutured to the skin, and an appliance is fitted. The subcutaneous bridge is secured at either end with a suture and cut short to allow enough for subsequent removal after 5–7 days.

Paper accepted 18 December 1995

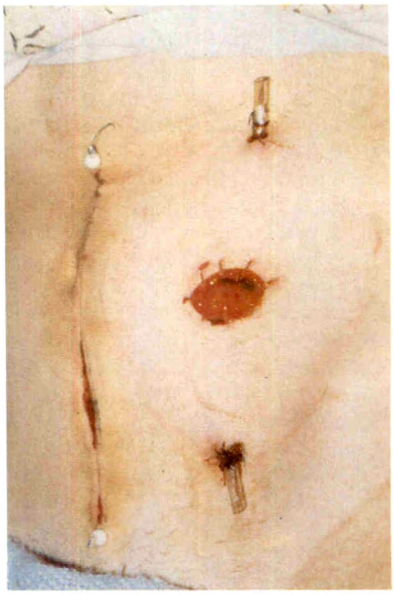

Fig. 1 Position of the Jacques catheter or nasogastric tube in a patient undergoing a loop colostomy

Discussion

The new method allows complete integrity of the mucocutaneous junction from the time of the creation of the stoma, thus preventing contamination of the peristomal subcutaneous tissue. It also permits positioning of an appliance flush with the stoma, making excoriation of the skin and leakage from the appliance less likely. The authors recommend the method for its aesthetic and practical appeal.

British Journal of Surgery 1996, 83, 1459–1462

Effect of different infusion regimens on colonic motility and efficacy of colostomy irrigation

J. M. GATTUSO, M. A. KAMM, C. MYERS, B. SAUNDERS and A. ROY

St Mark's Hospital, Northwick Park, Watford Road, Harrow HA1 3JU, UK
Correspondence to. Dr M. A. Kamm

The colonic motility response and short-term clinical effectiveness of colonic irrigation was studied in five patients with an end-colostomy, each of whom was studied on up to six occasions, using volumes of 500 and 1500 ml water infused under gravity and over a period of 2·5 and 5 min with a pump. The median baseline colonic luminal pressure was 14 cmH_2O and rose to 42 cmH_2O with a 500-ml infusion, and to 74 cmH_2O with a 1500-ml infusion. Irrigation induced high-pressure (over 200 cmH_2O) propagated waves which caused the efflux of colonic contents. These were more numerous after a 1500- than a 500-ml infusion (median 4·5 *versus* 2·0 respectively). There was no difference between the two volumes infused in the incidence of colostomy breakthrough before subsequent irrigation. Colostomy irrigation with 500–1500 ml water appears to produce intracolonic pressure rises that are safe. These volumes can be infused rapidly under gravity alone.

A colostomy is managed by one of the following: (1) natural spontaneous evacuation; (2) control of the colostomy output by drugs; and (3) colostomy irrigation[1]. The first two regimens lack good continence control, may require the use of a bulky appliance, and may produce a faecal odour. Colostomy irrigation is gaining in popularity as the safety of modern methods and the ability of even elderly patients to cope with the technique is recognized[2–4].

A major disadvantage is the time needed to perform irrigation, usually up to 1 h every 1–2 days. There is also little information regarding the ideal volume to be infused[5], and no information on the effect of the rate of inflow on the outcome of irrigation. These factors may be critical in obtaining the maximum benefit from irrigation.

The aims of this study were to determine (1) whether a large volume of fluid infusion produces a better result than a small volume infusion; (2) whether the infusion rate of the fluid is important in achieving a good result; (3) whether a pump is necessary to achieve rapid infusion, and whether this is beneficial and safe; (4) the intracolonic pressures during infusion at different volumes and rates; and (5) the relationship between the intracolonic pressures during colostomy irrigation and the outcome and occurrence of side-effects such as pain.

Patients and methods

Five patients (two women) of mean age 63 (range 59–66) years were studied. One patient (no. 1) had long-standing constipation (bowel action every 4–5 days) before operation; the rest had a pre-stoma bowel frequency of once per day. The patients had no other gastrointestinal problems. All had undergone abdomino-perineal resection with formation of an end-colostomy for rectal adenocarcinoma and were using irrigation as the preferred method of colostomy management. Patient details are shown in *Table 1*. The time spent performing colostomy irrigation was variable, but usually took up to 1 h, including 'cleaning up'. Three patients had difficulty with excessive flatus and four had occasional minor soiling, both occurring during the few hours before irrigation. Four patients graded the effectiveness of their usual irrigation technique as good or excellent, and one patient (no. 2) as fair to good. No patient was taking laxatives or other medication that affects gastrointestinal function significantly.

Table 1 Patient details

Patient no.	Age (years)	Sex	Usual volume (ml)	Interval between irrigations (h)	Break-through*
1	65	F	750–1500	48	None
2	64	M	1500	48	Once per week
3	62	M	650	24	Occasional
4	66	M	1500	48	Occasional
5	59	F	800	24	Yes (minor)

*Breakthrough was defined as any faecal discharge from the stoma between usual irrigations

Patients were studied when they would normally irrigate; in two patients this was 24 h and in three 48 h after the last irrigation. Patients had a light breakfast 4 h before the study, but there were no other dietary exclusions and no bowel preparation was used.

Colonoscopy was undertaken at 10.00 hours on each study day on unprepared bowel, without sedation. A guidewire was passed under direct colonoscopic vision into the proximal colon via the stoma. An ambulatory recording catheter (Gaeltec Ambulatory Recording System; Gaeltec, Dunvegan, Isle of Skye, UK) with three pressure transducers 10 cm apart was passed over the guidewire to lie 30–40 cm proximal to the stoma. The position of the catheter was confirmed by radiological screening after catheter placement and at the end of each study.

Recording of colonic pressures started once correct siting of the pressure transducers had been confirmed. Recording was undertaken: (1) for 30 min 'at rest'; (2) during a study meal of a sandwich and coffee, which was consumed within 20 min; (3) for 30 min after the meal; (4) during infusion of the irrigation water; and (5) for 60 min after the infusion.

After the post-meal period, a standard colostomy irrigation cone of the Laird type (Dansac, Fredensborg, Denmark) was inserted, and bags and tubing connected. Tap water at 37°C was run in under gravity, at the patient's head height, or using the pump.

Baseline pressures were measured during each component of the study. High-pressure contractile activity was also assessed, with high-pressure propagated waves being defined as a pressure rise above the baseline of more than 50 cmH_2O, involving two or more sensors, and progressing distally.

Paper accepted 12 January 1996

The postinfusion period was 'divided' into six 10-min periods. The output from the stoma was collected and measured during each of these periods.

The study was designed to investigate each subject on six separate study days. These involved: (1) 500 ml infused by gravity alone; (2) 500 ml infused over 5 min with a pump (Masterflex Pump Controller, model 7518-00; Barnant, Barrington, Illinois, USA); (3) 500 ml infused over 2·5 min by pump; (4) 1500 ml infused by gravity alone; (5) 1500 ml infused over 5 min by pump; and (6) 1500 ml infused over 2·5 min by pump If a particular volume of fluid entered the bowel in less than 5 min under gravity alone, then the 5-min pump infusion was not performed for that volume; the same procedure was adopted for the 2·5-min infusions.

After each study the patients returned home, but were asked to record any 'breakthrough' discharge of colonic contents before the next planned irrigation, in order to provide some guide as to the clinical effectiveness of each speed and volume of irrigation.

The study was approved by the Barts Hospital NHS Group Ethics Committee and all patients gave informed consent for each session.

Results

Colonoscopy and siting of recording catheter

All five patients completed the protocol, resulting in a total of 18 studies. At colonoscopy the colon contained formed stool in all patients. Colonoscopy was achieved without complication. The catheter was sited as proximally as possible, usually with the proximal tip in the transverse colon or splenic flexure and the distal pressure transducer at least 15 cm from the stoma. No significant catheter movement occurred in 14 studies as assessed radiographically. In four studies the distal transducer was extruded during the study, although the proximal two sensors remained in the colon.

Infusion of irrigate

Difficulty was experienced in initiating flow of the irrigate into the colon in some studies because of the anatomy of the stoma rather than colonic contraction. Once the infusion started, the rate of flow was always rapid. Times of infusion were recorded from when the flow started.

Using gravity alone, 500 ml was infused in a median of 2 (range 2–6) min and 1500 ml in a median of 5 (range 3–8) min.

All patients had an infusion of 500 and 1500 ml under gravity alone. Patients who had a slow infusion for a particular volume using gravity alone then had studies performed for that volume with the pump.

Pressure activity in the colon

Fig. 1 illustrates a typical manometric recording obtained during the studies. In all patients in all studies the baseline pressures did not change between the first three phases of the study: at rest, during and after the meal. The median baseline pressure of the five patients was 17 (range 3–50) cmH_2O.

In four of the 18 studies high-pressure propagated waves occurred during the preinfusion phases (*Fig. 2*).

After commencing the infusions the baseline colonic pressures increased, as shown in *Figs 3* and *4*. The increase in baseline pressure was not linearly related to either the volume infused or the rate of infusion. The median baseline pressure immediately before infusion was 14 (range 0–34) cmH_2O and rose to a median peak of 42 (range 14–101) cmH_2O with the 500-ml infusion and 74 (range 18–126) cmH_2O with the 1500-ml infusion.

The median change in baseline pressure after a 500-ml infusion under gravity was 11 (range 8–64) cmH_2O and that after a 1500-ml infusion under gravity 33 (range 11–102) cmH_2O. The pump was used to infuse 500 ml in 5 min in two patients, with pressure rises of 21 and 69 cmH_2O. In the same two patients the pump was used to infuse 500 ml in 2·5 min, with pressure rises of 12 and 63 cmH_2O. The pump was used to infuse 1500 ml in 5 min in two patients, with pressure rises of 42 and 139 cmH_2O. In two patients pressure rises of 37 and 68 cmH_2O occurred with a 2·5-min pump infusion. One 1500-ml pump infusion was terminated after 1300 ml because of abdominal discomfort. In this patient the peak pressure in the proximal transducer was 87 cmH_2O, an increase of 68 cmH_2O.

At the end of the infusion the cone was removed. There was usually an intermediate discharge of liquid followed by a number of effluent boluses containing solid and semi-formed faeces. These boluses occurred in association with recorded high-pressure propagated waves, as shown in *Fig. 5*. These high-pressure propagated waves often reached peaks of more than 200 cmH_2O. Occasional recorded high-pressure waves were not associated with any stoma output. *Table 2* shows the number of high-pressure propagated waves in each patient before and after infusion. The values for 'preinfusion' include a minimum

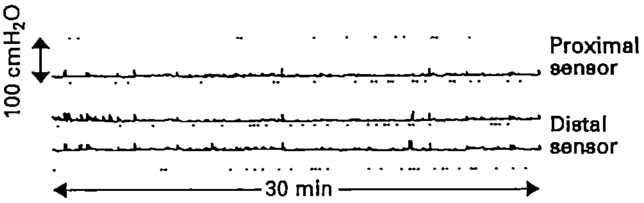

Fig. 1 Typical baseline pressure recording over a 30-min period Only a small amount of non-propagated segmenting activity is seen

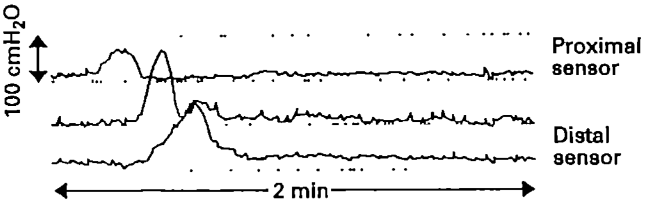

Fig. 2 One of the few preinfusion high-pressure propagated waves

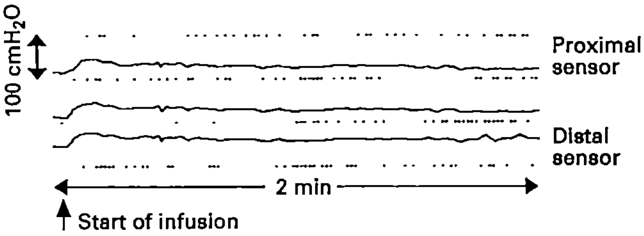

Fig. 3 Example of the effect of the infusion on baseline colonic pressures; 1500 ml was infused over 5 min by means of gravity. High-pressure waves have not yet been induced

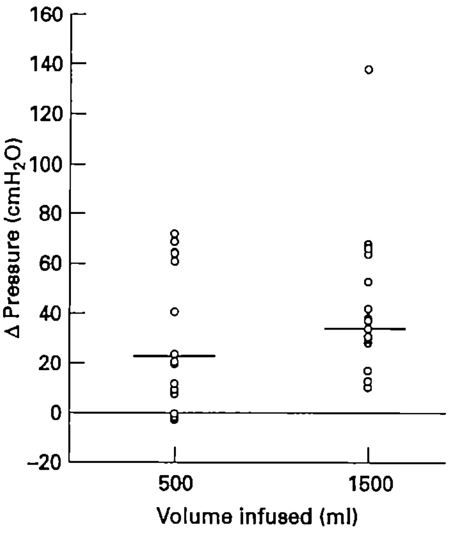

Fig. 4 Changes in intraluminal pressure produced by infusion of 500 and 1500 ml

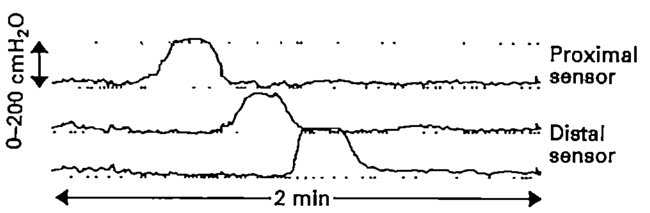

Fig. 5 Example of a high-pressure propagated wave in the postinfusion phase, induced by irrigation

Table 2 Median number of high-pressure propagated waves before and after infusion of 500 and 1500 ml tap water in 18 studies performed in five individuals

	Patient no.				
	1	2	3	4	5
Preinfusion (90 min)	0	0	0	4	0
Postinfusion (500 : 1500 ml) (min)					
0–10	1:3	>1*:0	0:2	2.3	1:3
11–20	0:1	>1*:0	1:3	1:0	2:1
21–30	0:1	>1*:0	1:2	2·0	0:1
31–40	0:0	0:2	0:0	0:0	0:0
41–50	0:0	0:2	0:0	0:0	0:0
51–60	0:0	0·0	0:1	0.0	0:0

*Data available for only two studies in this patient because of equipment failure

recording of 1·5 h; the postinfusion values are per 10-min period. The 1500-ml infusions were associated with a greater number of high-pressure propagated waves than 500-ml infusions (median 4·5 (range 3–8) *versus* 2·0 (range 1–9) respectively, $P = 0{\cdot}06$) but this did not reach statistical significance.

The baseline colonic pressure returned to preinfusion levels after the infusion was completed. This usually occurred within the first 10 min, and in all cases after 1 h.

Clinical effectiveness

No patient had any complications from the study. Subjectively patients considered that the 500-ml volume was not as successful as their usual volume or the 1500-ml infusion, although it was not practical to measure the actual amount of stool produced by irrigation. The output of irrigation fluid was measured, however, and was almost always found to be complete with either volume.

Discussion

Irrigation is a safe and effective method of colostomy management[2–4,6–9]. Perforation[10–15] is now rare as the irrigating cone[16] is used widely and complications such as burns[17,18] and subsequent stricture formation are avoidable.

The baseline colonic intraluminal pressures obtained in this study were similar to those reported elsewhere[19,20]. The light study meal did not induce any significant change in colonic pressures, reflecting the low calorific value of the meal[21]. The high-amplitude propagated waves have also been documented previously, both in anatomically normal colon[22,23] and in patients with a colostomy[24] in whom the introduction of the stimulant bisacodyl into the stoma produced progressive peristaltic activity similar to that observed with the introduction of water. These high-pressure events appear to be the manometric equivalent of radiographically observed mass movements. In the normal colon they occur approximately four to six times in 24 h[22,23]. After irrigation they were induced almost immediately, were most common in the first 10–20 min, and were associated with the effective evacuation of colonic contents.

Water infusion increased the basal colonic pressure. The pressure rise was greater with larger volumes, but was not greatly increased with a faster speed of infusion. Because the range of variables studied is likely to embrace the range of volumes and infusion speeds of everyday life, it is concluded that these speeds of infusion and volumes are safe.

This study has demonstrated that 1500 ml of infusate tends to result in a subjectively more effective 'irrigation' than 500 ml. In a study comparing the effectiveness of irrigation volumes 250, 500 and 1000 ml, 500 ml was preferred by the majority of patients. Objective parameters were similar, except for an increased incidence of faecal breakthrough with 250 ml[5].

The rate of infusion is usually easily adjustable with gravity alone, and this study suggests that there is no benefit from the use of a pump.

There are occasions when even experienced irrigators fail to obtain a satisfactory result from their usual irrigation technique. These data show that colostomy irrigation appears to work by the induction of high-pressure propagated waves. Further studies involving the addition of a stimulant to the irrigation fluid to achieve this may be useful[25–27]. Colostomy irrigation using 500–1500 ml can usually be achieved easily without the need for a pump.

Acknowledgements

The authors are grateful to Craig Medical Products for support, to Cathy Richards of the British Colostomy Association, and to stoma care sisters Peggy Claughton and Catherine Meadows.

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British Journal of Surgery 1996, 83, 1463–1467

Strengths and weaknesses of laparoscopic and open mesh inguinal hernia repair: a randomized controlled experimental study

L. F. HORGAN, J. C. SHELTON*, D. C. O'RIORDAN, D. P. MOORE, M. C. WINSLET and B. R. DAVIDSON

University Department of Surgery, Royal Free Hospital School of Medicine, and Interdisciplinary Research Centre in Biomedical Materials, Queen Mary and Westfield College, University of London, London, UK

Correspondence to: Mr B. R. Davidson, University Department of Surgery, Royal Free Hospital School of Medicine, Pond Street, London NW3 2QG, UK

There are no objective data available on the relative strengths of inguinal hernia repairs. The aim of this randomized controlled study was to measure the force required to disrupt laparoscopic and open mesh repairs in a porcine model. Eleven pigs had inguinal hernia repair following randomization to an open mesh group ($n = 5$) or a transabdominal preperitoneal laparoscopic group ($n = 6$). Four weeks after operation the pigs were killed and the pelvic girdles were mounted in a test jig on a mechanical testing machine. The applied disruption forces were measured and recorded. Mean(s.d.) force required to disrupt the normal inguinal canal ($n = 11$) was 68·6(30·1) N with no difference between groups. The open mesh repair required 110·3(41·4) N and the laparoscopic mesh 220·0(95·2) N. Both open and laparoscopic mesh repairs were stronger than the normal side ($P < 0·03$). The laparoscopic mesh repair was stronger than the open mesh repair ($P = 0·04$). This model provides a standardized method for mechanically testing inguinal hernia repairs in pigs. It confirms that both open and laparoscopic mesh hernia repairs are stronger than the non-herniated normal side at 4 weeks after operation. Laparoscopic mesh repair is stronger than open mesh repair. The weakest points of the repairs correlate well with those identified in clinical reports.

Inguinal hernia repair is the most commonly performed elective general surgical operation in the UK; it is estimated that 80 000 repairs are performed each year in England alone[1]. There is no consensus as to the optimal method of repair[2–5], and the recent advent of laparoscopic hernia repair has heightened the controversy[6,7]. The main problem with any type of repair is the recurrence rate, which is estimated as up to 20 per cent[8,9], and at present this is the parameter by which the long-term success of any repair is gauged.

The reasons why a repair fails are not clear; surgical technique[2], suture material[10], suture-line tension[11] and collagen abnormalities[12] have been implicated. The success of different repairs may be a consequence of a biomechanical advantage of one method over another but, in spite of the fact that inguinal hernia repair has been practised for almost two millennia[13], there has been little scientific evaluation of different inguinal hernia repairs. Recent controlled studies have attempted to address this issue but to date have reported only short-term outcomes[4,5,14]. Basic information, such as the strength of a particular hernia repair, is not available and hence the choice of hernia repair in the clinical setting has little scientific basis.

Laparoscopic inguinal hernia repair has been developed since the early 1990s[15]. The most commonly used technique at present is the transabdominal preperitoneal approach[16]. The open mesh repair has been recommended by some enthusiasts since the early 1960s[17] and it has now become more widely accepted[18]. The published recurrence rates and complications suggest it is a safe and effective method of hernia repair[19].

The authors hypothesized that the strength of a hernia repair may relate to subsequent recurrence rate. The present study compares the tensile strength of open and laparoscopic mesh inguinal hernia repair.

Paper accepted 31 May 1996

Materials and methods

All procedures were performed under the guidelines of the Animals (Scientific Procedures) Act 1986. Male pigs, each with a unilateral congenital indirect inguinal hernia (*Fig. 1*), were fasted overnight and premedicated with azaperone 0·1 ml/kg intramuscularly. An intravenous line was then inserted in the ear. Ketamine hydrochloride 5 mg/kg was used to induce anaesthesia. Following application of lignocaine spray to the larynx a size 5–7 cuffed endotracheal tube was inserted. The pigs were placed on a warming blanket and diathermy pad. The hindquarters were elevated on a wedge cushion to an angle of 25°. A pulse oximeter was connected to either the tail stump or the tongue and a rectal temperature probe was inserted. Anaesthesia using halothane, nitrous oxide and oxygen was given via a standard anaesthetic circuit. The abdomen and groin area were washed with chlorhexidine gluconate and two applications of povidone iodine. The area was then draped.

Experimental protocols

Each pig was randomized on the day of operation to either open or laparoscopic inguinal hernia repair. Five pigs were assigned to

Fig. 1 Post-mortem view of a left indirect inguinal hernia in the pig

the open group and six to the laparoscopic group. All operations were carried out by a single surgeon experienced in both techniques.

Open mesh repair. The contents of the hernia were reduced The anterior superior iliac spine (ASIS) and the pubic tubercle were identified. An incision of approximately 5 cm was made through skin and subcutaneous tissue to expose the external oblique muscle and the external ring. The external oblique was divided in the line of its fibres to expose the cord structures as far laterally as the deep ring. Care was taken to maintain haemostasis and to avoid damage to the ilioinguinal nerve. The cremasteric muscle was divided completely at the level of the deep ring. The hernial sac was identified, opened and transected. The vas and testicular vessels were dissected clear when possible The neck of the sac was then ligated in purse-string fashion. The distal portion of the sac was not excised. A polypropylene mesh was inserted, extending from just medial to the pubic tubercle to 2 cm lateral to the deep ring. It extended superiorly to 2 cm above the deep ring. The mesh was sutured to the inguinal ligament from medial to the pubic tubercle, with a 2/0 polypropylene suture running laterally towards the ASIS The mesh was secured with four interrupted sutures along the medial and superior sides. A slit in the lateral edge of the mesh allowed the cord structures to pass through. The resultant 'fishtail' was tacked with a single suture. A long-acting local anaesthetic, 10 ml bupivacaine hydrochloride 0·5 per cent, was administered close to the ilioinguinal nerve, the pubic tubercle and subcutaneously The external oblique was closed with a continuous 2/0 polyglactin suture. The subcutaneous tissues were approximated with two or three subcutaneous polyglactin stitches and the skin was closed with interrupted 3/0 polypropylene.

Laparoscopic inguinal hernia repair. A carbon dioxide pneumoperitoneum was established using a Veress needle via a supraumbilical stab wound. A 10-mm port (Ethicon Endo-Surgery, Edinburgh, UK) was then inserted through the same wound and the videotelescope was inserted. A 11–12-mm port and a 5-mm port were introduced under direct vision. They were inserted 6 cm to each side of the umbilicus using the Z technique[20]. All ports used were disposable. Any contents within the hernia were reduced. Anatomical landmarks were located. The peritoneum lining the hernial sac was incised in elliptical fashion using a scissors and graspers (Ethicon Endo-Surgery). The incision was extended both medially to the pubic tubercle and laterally toward the ASIS. Two peritoneal flaps were developed – one superiorly, one inferiorly – allowing space for the mesh. Haemostasis was continuously checked and care was taken not to damage the flaps. A polypropylene mesh was inserted via the 11–12-mm port and placed in position so that it extended from the pubic symphysis to the ASIS and covered the internal inguinal ring and the femoral area. It was kept in position with six staples. No staples were used on the inferior margin over the area occupied by the iliac and testicular vessels and the vas deferens. On the superior margin care was taken to avoid the inferior epigastric vessels. No staples were placed on the lateral side or within 1·5 cm of the ASIS to avoid injury to the lateral cutaneous nerve of the thigh. The edges of the peritoneum were then approximated and closed with staples Haemostasis was confirmed and the operating ports were removed under direct vision to ensure there was no bleeding. The telescope was withdrawn halfway out of the umbilical trocar and the trocar itself withdrawn slowly to check for bleeding or herniation. The 10-mm and 11–12-mm port sites were closed with 2/0 polypropylene. Bupivacaine hydrochloride (0·5 per cent, 10 ml) was injected into the wounds.

The skin was closed with interrupted 2/0 polypropylene sutures. The pigs were then kept in the recovery unit until they were fully mobile and drinking, which took less than 60 min for each animal. Over the subsequent 4 weeks the pigs were observed for hernia recurrence and local wound complications. After 4 weeks the pigs were premedicated with azaperone and a lethal 30-ml dose of pentobarbitone sodium 200 mg/ml was administered intravenously. At autopsy the pelvic girdle with lower abdominal wall was removed intact.

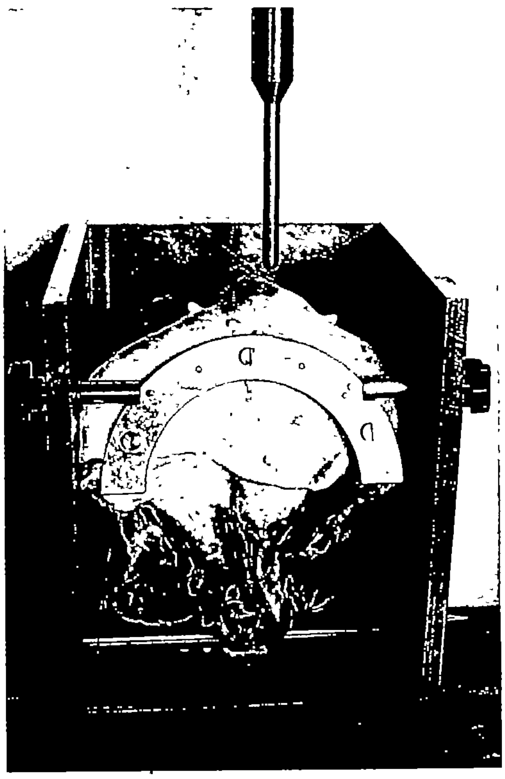
Fig. 2 Pig pelvis mounted in testing jig with rod in place before testing

Mechanical testing

The repairs were tested within 2 h of death. A three-point aluminium alloy fixator jig was developed to allow stable mounting of pelvises from pigs weighing up to 50 kg. The prepared pelvis was mounted in the jig by rigidly fixing the lumbar spine and sacrum and clamping the anterior abdominal wall at a preset tension of 200 N (*Fig. 2*). The mounted pelvis was positioned within a screwdriver mechanical testing machine (Model 6025; Instron, High Wycombe, UK).

Each repair was disrupted using a metal rod with a hemispherical tip of 10 mm diameter which was advanced along the inguinal canal from within the pelvis. The rod was advanced from deep to superficial at a constant rate of 0·5 mm/s and the maximum force measured on a 1-kN load cell The direction of the inguinal canal was previously determined radiographically Both the repaired and the normal non-herniated sides were tested. The specimens were then examined macroscopically to determine where disruption had occurred.

Results

The group characteristics are shown in *Table 1*. The time taken to perform a laparoscopic inguinal hernia repair in the pig was significantly less than that for open repair ($P<0·05$; *Table 1*). There was no significant difference in preoperative or final weights, defect size, mesh size or recovery time between the groups.

There were no clinical recurrences during the 4 weeks following surgery in either group and no disrupted repairs were seen before stress testing. Stress testing was performed in all 11 animals. *Fig. 3* shows a typical graph, obtained during testing, where the applied force increased as the metal rod travelled down the inguinal canal in both an open and a laparoscopic repair. The slope of the graph becomes steeper as the elastic limit of the tissue is reached. The sudden drop that follows represents the complete disruption of the repair. Irreversible deformation occurs if the elastic limit is exceeded ('yield point') and a further load increase leads to rupture of the tissue ('break point').

Table 1 Group characteristics

	Laparoscopic ($n=6$)	Open ($n=5$)
Operating time (min)	42·5 (30–55)*	60·0 (45–75)
Defect size (cm^2)	3·3 (2–4)	2·6 (1–4)
Mesh size (cm^2)	19·3 (17–24)	13·5 (8–20)
Preoperative weight (kg)	13·6 (10–20)	12·0 (9–20)
Final weight (kg)	30·3 (24–50)	27·0 (24–30)
Recovery time (min)	47 (30–60)	53·0 (45–60)

Values are mean (range) $^*P<0·05$ *versus* open repair (Student's *t* test)

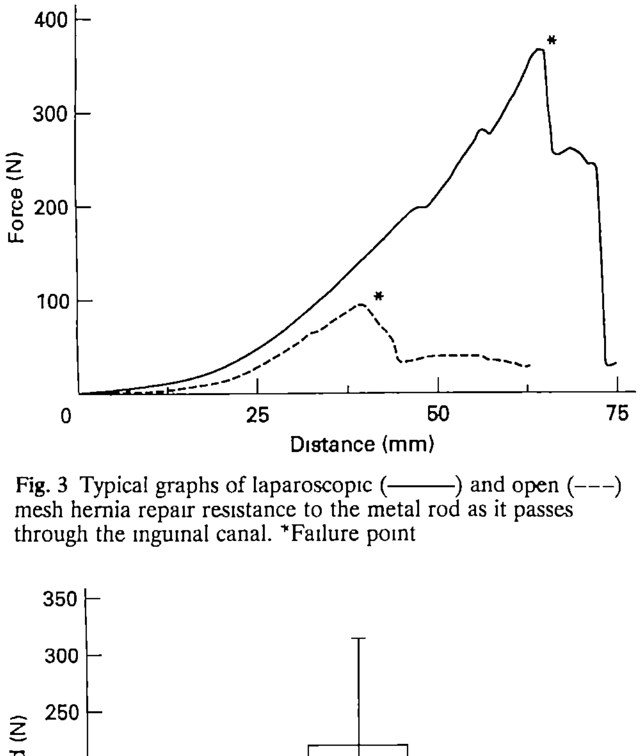

Fig. 3 Typical graphs of laparoscopic (———) and open (- - -) mesh hernia repair resistance to the metal rod as it passes through the inguinal canal. *Failure point

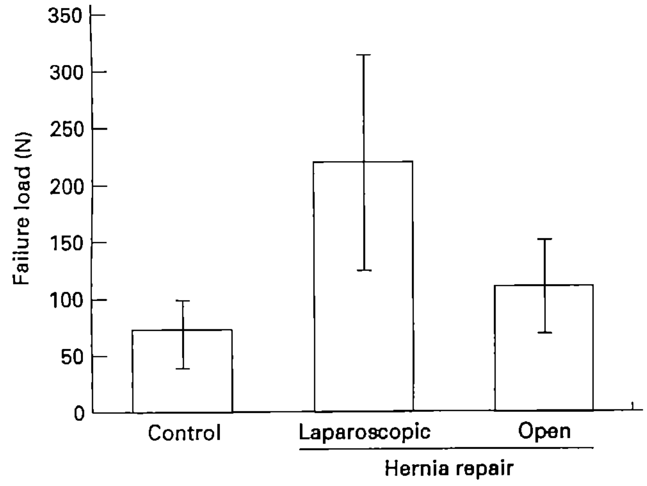

Fig. 4 Mean load required to disrupt the normal inguinal canal, and laparoscopic and open mesh repairs. Error bars represent one standard deviation

The open repair was seen to fail at lower loads than the laparoscopic repair. In the latter there were some small steps in the loading curve, where small partial failures occurred, although these were not classified as the failure load or break load.

The open hernia repair (mean(s.d.) disruption force 110·3(41·4) N) was significantly stronger than the normal side (68·6(30·1) N); $P=0·02$) but the laparoscopic hernia repair (220·0(95·2) N) was significantly stronger than both the open repair ($P=0·04$) and the normal inguinal canal ($P=0·01$; *Fig. 4*).

After testing, the specimens were excised and examined macroscopically to determine the nature of the stress-induced disruption points. Three of the five open repairs showed disruption as a result of upward displacement of the mesh and the abdominal wall *en bloc*. This was caused by avulsion of the anterior abdominal wall and inguinal ligament from their insertion on the pelvis. This eventually allowed the probe to travel down the deformed femoral canal. The fourth failed because the inferomedial corner of the mesh became detached over the pubic tubercle and the fifth because the anterior abdominal wall ruptured around the superior border of the mesh.

The cause of disruption in four of the six laparoscopic repairs was detachment of the mesh at the inferomedial border. The fifth mesh gave way at the superior margin and in the sixth the mesh was completely detached and pushed down the inguinal canal.

Examination showed that the mesh remained intact throughout testing in both the laparoscopic and open groups.

Discussion

Testing the repairs to destruction required an animal model. The pig was chosen because some breeds have a high prevalence of congenital indirect inguinal hernia[21]. Inguinal hernia occurs in up to 5 per cent of the Large White/Landrace breed used in this study. The pig has been used in other studies of hernia repair[22-24] and is suitable because (1) the anatomy of the inguinal region is similar to that of the human, (2) it is large enough to allow laparoscopic procedures to be performed and (3) it can tolerate general anaesthesia and recovery well. Scrotal hernias in pigs are usually treated by castration[25] and although the laparoscopic repair has been described[22] this paper is the first report of open hernia repair in a pig. The open repair was difficult particularly when dissecting the delicate hernial sac from the cord and hence the open procedure took longer to perform than the laparoscopic repair.

The present study provides an objective method of measuring the force required to disrupt a hernia repair. In designing this study an attempt was made to recreate the pressure to which a repair would be subjected. Feasibility studies were performed which sustained intra-abdominal pressure at 138 Pa for periods of 5 min. However, no damage to the hernia repairs was seen. Applying pressure directly to the mesh was considered to be the best method of loading the repair. Testing to destruction exposes weak points that would be difficult to predict in a clinical study.

The laparoscopic inguinal hernia repair was found to be significantly stronger than the open repair and the normal side in the porcine model. The open repair was also stronger than the normal inguinal canal. The strength of both repairs in comparison to the normal side confirms the efficacy of polypropylene mesh for strengthening the inguinal canal during hernia repair. The difference in strengths between laparoscopic and open repair may be explained by the position of the mesh in relation to the defect. Once an open repair started to fail, where the mesh was superficial to the defect, then failure proceeded rapidly. In the laparoscopic repair the internal placement allowed greater overall strength even if some early failure had occurred.

When the laparoscopic repair disrupted under testing, this usually occurred as a result of detachment of the mesh. Four of the six meshes detached at the inferomedial border; this is an area where adequate overlap is vital. This weak point has been noted in recent papers looking at recurrence following laparoscopic repair[26,27]. One detached from the superior border and again sufficient overlap of the defect is mandatory here. The potentially correctable weak point in the open mesh repair is where the inferomedial border of the mesh overlies the pubic tubercle. This area failed under testing in one of the experimental repairs. This has been noted by others[19] in the clinical situation.

Previous biomechanical studies have attempted to devise objective criteria to compare hernia repairs. Stress testing of the transversalis fascia has suggested an inherent weakness in the fascia which predisposes to herniation with loading curves similar to those produced in the present study[28]. Further studies have suggested a defect in collagen synthesis[12,29,30]. Previous assessments of suture tension in the Bassini repair and the aponeurotic repair have suggested that a tension-free repair could withstand the stress induced by intra-abdominal pressure[11]. The bursting strengths of mesh and sutured repairs of the abdominal wall[31,32] and breaking points of different mesh–staple combinations[33] have been evaluated previously. This study is the first to design a model to test the strength of hernia repairs *in situ*.

Whether the greater strength of the laparoscopic hernia repair will translate into better long-term results and a lower recurrence rate remains to be seen. It would seem likely that the strongest repair at 4 weeks after an operation should have an advantage. Further studies looking at other time periods and methods of repair are required. This model for testing hernia repairs may highlight unsuspected weak points and allow modifications for clinical use.

Acknowledgements

The authors thank Mr R. Morris (statistician) and Mr A. Snook (Medical Engineering) for their help, and Ethicon Endo-Surgery, Edinburgh, UK, which funded this study.

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British Journal of Surgery 1996, 83, 1467

Surgical workshop

A new way to prevent leakage of glycine during endoscopic transanal resection of rectal lesions

F. ABBASAKOOR and R. B. STEPHENS

Department of Surgery, St James's Hospital, James's Street, Dublin 8, Ireland

Correspondence to: Mr R. B Stephens

Since endoscopic transanal resection was first described by Lindenschmidt *et al.*[1] in 1977, it has earned a limited but valuable place in colorectal surgery. Satisfactory long-term outcome may be achieved for patients with benign rectal lesions and acceptable results have been obtained for those in whom conventional surgery would carry unacceptable risks, notably the elderly with advanced cancer or those with severe concurrent illness[2].

Leakage of glycine during the procedure can be a problem. This paper describes the use of a modified endotracheal tube in conjunction with existing urological resectoscopes to overcome this problem.

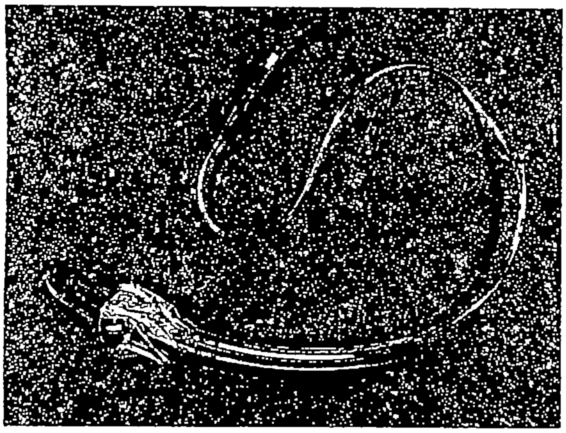

Fig. 1 The modified endotracheal tube with preservation of the insufflator channel

Surgical technique

The patient undergoes full bowel preparation before operation to minimize the potential risk of perforation. Antibiotic prophylaxis is administered intravenously at the time of induction of anaesthesia. The operation is performed under general or spinal anaesthesia with the patient in the lithotomy position.

A standard 24-Fr urological resectoscope (Circon, American Cystoscope Manufacturing Incorporated, Stanford, Connecticut, USA) with its 30° telescope is inserted through an endotracheal tube that has been modified by halving its length, while preserving the channel to insufflate the cuff (*Fig. 1*). This is simply carried out with a pair of heavy scissors. A size 10 endotracheal tube (Mallinckrodt ID 10; Mallinckrodt Medical, Athlone, Ireland) fits the resectoscope perfectly. The cuff prevents leakage of glycine and its size can be altered to fit the anal opening, usually with 15–20 ml of air.

Discussion

Endoscopic transanal resection needs to be performed under low pressures of 20–30 cm glycine to minimize the risks of perforation, and some peranal leakage is therefore a useful safety valve. However, major leakage and insufficient rectal distension is a particular problem when using the 24- or 27-Fr urological resectoscopes. Reliance on anal sphincter tone alone has been found to be adequate by some[3], but in the present authors' experience it is not always reliable for achieving good rectal filling at low pressures. The use of a specially adapted Lord's dilator has been described[4] to prevent leakage. Endoscopic transanal resection of rectal lesions is increasing in popularity. The ability to perform this operation in any hospital with existing urological instruments and a modified endotracheal tube as a simple, cheap and effective way of preventing leakage is appealing.

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Paper accepted 5 January 1996

British Journal of Surgery 1996, 83, 1468–1472

Effects of vertical-banded gastroplasty on bone and mineral metabolism in obese patients

T. CUNDY, M. C. EVANS, R. G, KAY*, M. DOWMAN, D. WATTIE and I. R. REID

*Departments of Medicine and *Surgery, University of Auckland School of Medicine, Auckland 1, New Zealand*
Correspondence to. Dr T. Cundy

The surgical treatment of obesity can have adverse effects on bone, but there are few published data on the effects of vertical-banded gastroplasty. Serial measurements of bone mineral density at the lumbar spine and three upper femoral sites, using dual-energy X-ray absorptiometry, and also of biochemical indices of bone and mineral metabolism at intervals up to 2 years after operation were performed in 18 patients with morbid obesity who had vertical-banded gastroplasty. Bone mineral density measurements were also made in age- and sex-matched non-obese controls. Bone density before operation was significantly greater in the obese than in the controls ($P<0\cdot02$ at all sites). The obese patients lost weight rapidly after vertical-banded gastroplasty (mean weight loss 29 kg at 1 year, $P<0\cdot001$). This was accompanied by a measurable loss of bone density from the trochanter and Ward's triangle sites in the upper femur ($P<0\cdot05$), but not from the lumbar spine. Bone density values remained stable over 14 months in the controls. Hydroxyproline excretion increased significantly ($P<0\cdot005$), indicating an increase in bone resorption. Alkaline phosphatase levels decreased significantly ($P<0\cdot001$), but this probably represents the reversal of hepatic steatosis. There was no evidence of hyperparathyroidism or vitamin D deficiency. In conclusion, vertical-banded gastroplasty causes modest bone density loss from femoral sites, but not the lumbar spine. The difficulties of assessing bone density changes in the obese are discussed.

Body-weight is an important determinant of bone mineral density, and overweight people have been shown consistently to have higher bone density than the non-obese[1–4]. There is, however, considerable uncertainty about whether weight loss in the obese is accompanied by loss of bone density. Some studies have reported that there is little or no effect of weight loss on bone density[5,6], whereas others have found variable degrees of bone loss[7–11]. In some of these studies the reported rate of bone loss has been remarkably rapid[10,11].

Vertical-banded gastroplasty is one of the most effective and rapid ways to help the obese to lose weight, but to the authors' knowledge only one of the published studies of the effect of weight loss on bone density has included any patients having this procedure[7]. Osteoporosis and secondary hyperparathyroidism are common sequelae of partial gastrectomy for ulcer disease[12,13] and may also occur after gastric bypass procedures for morbid obesity[14]. It is therefore possible that vertical-banded gastroplasty could result in significant bone loss and hyperparathyroidism with important long-term consequences. In this study bone density and biochemical indices of mineral metabolism were prospectively measured in a group of morbidly obese patients undergoing vertical-banded gastroplasty.

Patients and methods

Patients and surgical technique

Eighteen patients were studied before and after gastric restriction surgery for morbid obesity. Fourteen patients were premenopausal, two postmenopausal and two were men. Mean age was 37 (range 23–54) years The operation performed in each patient was vertical-banded gastroplasty in which a gastric pouch of 20 ml was created[15]. Patients were counselled extensively before the procedure and adhered to a weight-reducing diet for several weeks before the operation.

Bone density measurements were made at the time of operation and at 6, 12 and 24 months after surgery. At these times patients were weighed wearing light indoor clothing using electronic scales, and blood and urine samples were collected for biochemical analyses. All patients continued regular supervision from a dietitian in the postoperative period and were also prescribed a daily supplement of one multivitamin tablet (containing 7·5 μg calciferol). Calcium supplements were not prescribed.

Bone density measurements in the obese patients were compared with those from 18 control subjects matched individually for age and sex, but not for body-weight (*Table 1*). Two bone density measurements from the controls, a mean of 14 months apart, were made.

Bone density measurements

Bone mineral density was measured in the lumbar spine (posteroanterior projection) and at three sites in the upper femur (femoral neck, trochanter and Ward's triangle) using dual-energy X-ray absorptiometry (Lunar DPX-L, software version 1·2, Lunar Corporation, Madison, Wisconsin, USA). The precision of these measurements in the authors' laboratory is 1·0 per cent for the lumbar spine, 1·4 per cent for the femoral neck, 2 9 per cent for Ward's triangle and 1·6 per cent for the trochanter.

Biochemical measurements

The biochemical assessments (obese patients only) included total plasma calcium (adjusted for plasma albumin) and plasma concentrations of phosphate, magnesium, 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D, parathyroid hormone and (in women only) free testosterone[16]. The plasma activities of the enzymes aspartate aminotransferase (AST), γ-glutaryl transpeptidase (γGT) and alkaline phosphatase were also measured. Hydroxyproline excretion was assessed in a fasting urine sample and expressed as the hydroxyproline : creatinine molar ratio.

Statistical analysis

Student's *t* test for paired samples was employed for within-group comparisons. Differences between patients who had gastroplasty and controls were also assessed by the paired *t* test

Paper accepted 12 December 1995

on the matched pairs of patients. Correlations were calculated by Pearson's method. Results are given as mean and 95 per cent confidence interval (c.i.) unless otherwise stated. The study was approved by the local research ethics committee.

Results

Gastric restriction surgery was successful in reducing weight in most patients. Mean weight loss was 24 (range 1–39) (95 per cent c.i. 20–29) kg at 6 months, 29 (range 3–70) (95 per cent c.i. 22–36) kg 1 year and 24 (range 7–39) (95 per cent c.i. 18–30) kg at 2 years (all values $P < 0·001$ *versus* preoperative weight), representing a mean weight loss of 21·3 per cent at 6 months, 24·9 per cent at 1 year and 21·4 per cent at 2 years. Expressed as the percentage excess over ideal body-weight, this fell

Table 1 Baseline demographic, anthropometric and bone mineral density values in patients undergoing gastric restriction surgery and in control subjects

	Sex (F:M)	Age (years)	Height (m)	Weight (kg)	BMI (kg/m²)	Excess body-weight (% of ideal)	Bone mineral density (g/cm²) Lumbar spine	Femoral neck	Ward's triangle	Trochanter
Gastric restriction surgery (*n* = 18)	16:2	37 (32–42)	1·65 (1·60–1·70)	118 (109–127)	43·4 (40·8–46·0)	108 (96–120)	1·425 (1·299–1·551)	1·144 (1·057–1·231)	1·081 (0·958–1·204)	1·026 (0·952–1·100)
Controls (*n* = 18)	16:2	37 (33–41)	1·66 (1·63–1·69)	64 (57–71)	23·3 (21·4–25·3)	10 (1–18)	1·203 (1·137–1·269)	0·979 (0·900–1·058)	0·885 (0·796–0·974)	0·831 (0·771–0·891)
*P**		n.s.	n.s.	<0·001	<0·001	<0·001	<0·002	<0·02	<0·01	<0·001

Values are mean (95 per cent confidence interval). BMI, body mass index; n.s., not significant. *Student's *t* test

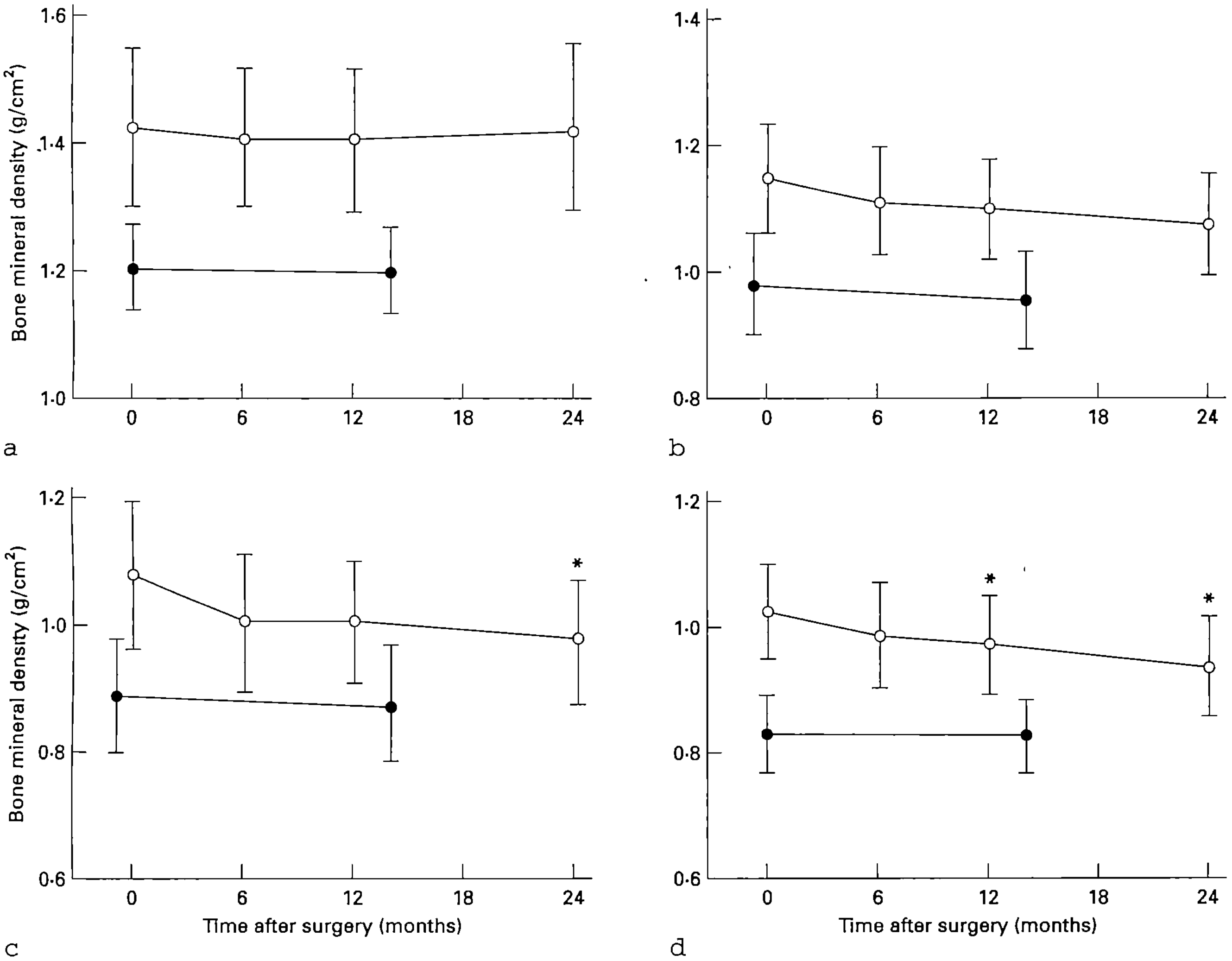

Fig. 1 Sequential changes in bone mineral density at **a** the lumbar spine, **b** the femoral neck, **c** Ward's triangle and **d** the trochanter in patients who had vertical-banded gastroplasty (○) and in control subjects (●). Results are mean (95 per cent confidence interval). *$P < 0·05$ *versus* initial value, paired *t* test

Table 2 Biochemical findings

	Laboratory normal range	Before operation	Time after operation		
			6 months	1 year	2 years
Calcium (mmol/l)	2·15–2·55	2·32 (2·28–2·36)	2·32 (2·27–2·37)	2·26 (2·20–2·32)	2·21 (2·17–2·25)§
Phosphate (mmol/l)	0·8–1·4	1·14 (1·08–1·20)	1·17 (1·10–1·24)	1·17 (1·09–1·25)	1 23 (1 15–1·31)
Magnesium (mmol/l)	0·8–1·0	0 81 (0·75–0·87)	0·84 (0·81–0·87)	0 83 (0·78–0·88)	0·80 (0 76–0·84)
Parathyroid hormone (pmol/l)	1–5	2·5 (1 9–3·2)	2·4 (1·8–3 0)	2·5 (2·0–3·0)	2·4 (1 7–3 1)
25-Hydroxy vitamin D (μg/l)	14–76	25·1 (21·5–28·6)	29·9 (24·5–35·3)*	30 0 (22·8–37·2)	30 5 (26 2–34·8)††
1,25-Dihydroxy vitamin D (pg/l)	20–60	44·5 (36·3–52·7)	41·8 (34·9–48·7)	45 7 (37·1–54·3)	45·7 (36·6–54·8)
Alkaline phosphatase (units/l)	25–100	77 (67–87)	68 (57–79)†	60 (51–69)**	61 (52–70)**
AST (units/l)	5–45	19 (15–23)	18 (15–21)	14 (12–17)†	15 (11–19)
γ-GT (units/l)	0–50	35 (24–46)	23 (9–37)**	15 (12–18)**	21 (9–33)‡
Hydroxyproline : creatinine (molar ratio $\times 10^3$)	15–30	23 (20–26)	35 (29–41)‡	32 (26–38)‡	23 (18–28)
Free testosterone (pmol/l)	8–58	36 (26–46)	25 (18–32)	23 (18–28)†	25 (19–31)*

Values are mean (95 per cent confidence interval). Free testosterone was measured in female patients only. AST, aspartate aminotransferase; γ-GT, γ-glutaryl transpeptidase *$P<0{\cdot}05$, †$P<0{\cdot}02$, ††$P<0{\cdot}01$, ‡$P<0{\cdot}005$, §$P<0\ 002$, **$P<0{\cdot}001$ *versus* initial values (paired t test)

from a mean of 108 per cent before operation to 64 per cent at 6 months, 56 per cent at 1 year and 63 per cent at 2 years. Mean body-weight remained stable in the controls.

At baseline, bone density was significantly greater in the obese patients than in the controls at all sites (*Table 1*), and it remained stable at all four sites in the control subjects. Patients undergoing gastroplasty showed some loss of bone density from the femoral sites, particularly from Ward's triangle (mean loss 3·9 (95 per cent c.i. 0·3–7·5) per cent at 2 years, $P<0{\cdot}05$) and the trochanter (mean loss 4·0 (c.i. 0·5–7·5) per cent at 1 year and 4·8 (c.i. 0·2–9·4) per cent at 2 years, both $P<0{\cdot}05$, *Fig. 1*). The loss of bone from the trochanter was significantly greater in the eight patients who lost the most weight by 6 months (25 per cent or more of presurgery body-weight) than in the ten who lost 21 per cent or less ($P<0{\cdot}02$ at 1 year, $P<0{\cdot}005$ at 2 years, Students t test) but there were no direct correlations between the changes in bone density and body-weight.

Mean values for lumbar spine bone mineral density as a whole did not change over the 2-year follow-up in the patients who had gastroplasty. Only three patients had decreases of more than 5 per cent in lumbar spine bone density. These were the two men and one premenopausal woman aged 36 years at the time of surgery; the woman became amenorrhoeic shortly after her operation and measurements of plasma follicle-stimulating hormone confirmed that she had developed premature menopause. She took hormone replacement therapy in the second year of the study.

Sequential measurements of biochemical parameters in the obese patients undergoing gastroplasty showed significant reductions in plasma calcium at the 2-year point only, and in free testosterone. Plasma alkaline phosphatase activity also decreased significantly, as did the activity of the liver-derived enzymes γGT and AST. The fasting urine hydroxyproline : creatinine ratio increased transiently, but returned to baseline levels by 2 years. There was also a small increment in mean plasma 25-hydroxy vitamin D. Plasma concentrations of magnesium, phosphate and 1,25-dihydroxy vitamin D did not change (*Table 2*).

Discussion

This study has confirmed that bone mineral density is increased in the obese and that vertical-banded gastroplasty is highly effective at inducing weight loss in most patients. Although the mean weight loss was impressive, the changes in bone density were modest, with significant losses from the trochanter and Ward's triangle sites at the hip, but no loss from the lumbar spine. Despite the small number of patients the authors are able to demonstrate some relationship between bone loss and weight loss, as the patients who lost most weight had the greatest decline in bone density at the trochanter.

The literature examining the effects of weight loss on bone is difficult to summarize, in part because the degree of weight loss attained has differed between studies but also because the sites at which bone has been measured, the duration of the studies, the type of densitometers and their software, and the way of expressing the results (bone mineral content or bone mineral density) have also varied. Even considering these variables some of the findings are difficult to reconcile. For example, in the prospective study of Krolner *et al.*[7], there was a mean loss of 28 per cent body-weight and 7·2 per cent bone mineral content of the lumbar spine, as measured by dual photon absorptiometry in 14 patients who had either gastric bypass or vertical-banded gastroplasty. In the study by Jensen *et al.*[11], in which 52 patients consumed a very low calorie diet, mean weight loss was 12·5 per cent over 15 weeks and was accompanied by a decrease of 6·9 per cent in the bone mineral content of the trunk, as measured by dual-energy X-ray absorptiometry. These results contrast markedly with the findings in the present study of unchanged spinal bone density over 2 years, despite massive weight loss. Studies of forearm bone density changes have also yielded disparate results[5,9].

Such discrepancies suggest that considerable methodological problems arise when measuring bone density (or mass) in the obese. These have been demonstrated in several studies using absorptiometry techniques[5,17–20]. The thickness of soft tissue around a bone reduces the proportion of X-rays (or photons) surviving attenuation, and interferes with bone edge detection. The effect of fat may vary according to the quantity present and its distribution within the abdomen, and also varies between different makes of densitometer[19], and with different versions of software. Increased thickness of soft tissue can also change the apparent area of bone measured, which presumably explains the surprising differences between changes in bone mineral content and bone mineral density noted in some studies[10]. In general, when bone density results are reported, the bone 'loss' associated with weight loss is much less marked[6]. Manufacturers of the software for commercial densitometers have recognized these artefacts and attempted to correct them in recent versions such as the one used in this study (R. Mazess, Lunar Corporation, personal communication). However, it remains possible that some artefacts persist. Experiments in which lard is layered on to the abdomen, or a phantom, to simulate the effects of obesity[8,11,20] may not always be effective in defining such artefacts, because the effects of fat on bone mineral measurements depend on its regional distribution[19].

The loss of bone observed appears to have resulted from an increase in bone resorption, as indicated by the increased excretion of hydroxyproline, an effect also noted in other studies[6,9,10]. Weight loss in the obese may also be accompanied by increases in markers of bone formation[6,9], indicating that bone turnover is increased during weight loss. In the present study alkaline phosphatase activity decreased significantly, but this cannot be interpreted as a reduction in bone formation, as γGT and AST also declined, suggesting that the reduction in alkaline phosphatase was probably the result of a reversal of hepatic steatosis. Although a decrease in plasma calcium was noted at the 2-year point, neither parathyroid hormone nor 1,25-dihydroxy vitamin D were increased at any stage in the study. These results provide assurance that the bone sequelae of partial gastrectomy, gastric bypass and intestinal bypass procedures are unlikely to complicate vertical-banded gastroplasty. However, it should be noted that these problems characteristically present several years after surgery[12–14,21], so that follow-up for longer than 2 years would be necessary to ensure that late bone disease did not occur.

In the absence of hyperparathyroidism, the stimulus to increase bone resorption is not clear. The reduction in free testosterone in the female patients (presumably a result of decreased peripheral androgen production) may have some relevance, but the distinct pattern of loss that was observed (femur greater than lumbar spine) suggests that the bone loss was related to decreased weight bearing rather than changes in sex steroids. There is evidence from cross-sectional studies (in older men and women) that the relationships between body-weight and bone density are strongest at weight-bearing sites[22]. Most patients in the present study were premenopausal women and it is possible that the effects of the procedure may differ in postmenopausal women.

In previous studies, the authors[23,24] have highlighted the strong relationships between bone density and total body fat in both premenopausal and postmenopausal women. The relatively small reduction in bone density noted in this study, despite the large loss of weight, suggests that the relationship between fat and bone density may not be linear over the wide range from normal to the morbidly obese. It should be remembered that this procedure did not turn obese patients into normal weight individuals. One year after operation the patients remained significantly heavier than the control subjects (mean weight 89 *versus* 64 kg, $P < 0{\cdot}001$), and some 56 per cent above ideal body-weight.

It is concluded that vertical-banded gastroplasty for weight reduction in the obese is accompanied by loss of bone from the hip sites but not the spine. The bone loss appears to result from a transient increase in bone resorption. There is no evidence that vertical-banded gastroplasty induces secondary hyperparathyroidism, vitamin D deficiency or hypomagnesaemia.

Acknowledgements

This study was supported by the Health Research Council of New Zealand.

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British Journal of Surgery 1996, 83, 1473–1477

Selective approach to the treatment of oesophageal cancer

T. JUNGINGER and P. DUTKOWSKI

Department of General and Abdominal Surgery, University of Mainz, Germany
Correspondence to: Professor T Junginger, Klinik f Allgemein-und Abdominalchirurgie, Universitat Mainz, Langenbeckstrasse 1, 55 101 Mainz, Germany

Between September 1985 and December 1994, 322 patients with oesophageal cancer were treated. Of the 190 patients who underwent operation, 173 had an oesophageal resection; in 124 this was performed as an abdominothoracic resection and in 49 by the transhiatal approach. The assessment of radicality after histological examination revealed a curative (R_0) resection in 121 patients (70 per cent) and a palliative (R_1–R_2) resection in 52 (30 per cent). Prognosis was correlated with the extent of mediastinal lymph node dissection. In 77 patients with stage pT_{1-3} pN_{0-1} pM_0 the 5-year survival rate was 40 per cent after abdominothoracic resection with two-field lymph node dissection and zero after transhiatal resection ($P = 0{\cdot}01$). The authors propose a differentiated surgical approach involving abdominothoracic resection with two-field lymph node dissection for patients with limited tumours (pT_{1-3} pN_{0-1} M_0) if the operative risk is tolerable. Transhiatal resection appears to be effective only in patients with early tumours (Union Internacional Contra la Cancrum stage 0).

There is controversy about the prognostic influence of the surgical procedure in patients with oesophageal cancer. Bolton *et al.*[1] and Goldminc *et al.*[2] reported no prognostic difference between transthoracic and transhiatal approaches. However, there is evidence for improvement in survival for certain tumour stages following three-field lymph node dissection[3]. In addition, a European multicentre study in patients with submucosal oesophageal cancer[4] showed a better prognosis after transthoracic than following transhiatal resection.

In the authors' institution the abdominothoracic approach is used routinely, but patients with a higher operative risk because of pulmonary complications undergo transhiatal resection. The aim of this prospective non-randomized observational study was to determine whether extended lymphadenectomy in transthoracic resection produces an improvement in outcome. An important question is whether the different indications for the two operative procedures limit the comparability of the groups. Special attention was therefore paid to structural similarity by univariate and multivariate analysis. Independent prognostic factors were identified by regression analysis.

Patients and methods

Between September 1985 and December 1994, 322 patients with histologically proven squamous carcinoma or adenocarcinoma of the oesophagus were treated. Some 109 patients already had multiple distant metastasis at admission and underwent palliative non-surgical treatment. Twenty-three patients with an irresectable tumour had a palliative bypass procedure (endotubus). Of the 190 patients who underwent operation, 17 had an exploratory laparotomy which showed a more advanced tumour than expected. In two cases an endotubus was placed at this time.

Prognostic factors were analysed in the remaining 173 patients, who underwent primary resection. This was performed in 124 cases by the transthoracic approach and in 49 by the transhiatal approach (*Fig. 1*).

Transthoracic resection was carried out using the abdominal and right thoracic route with *en bloc* oesophagectomy and proximal gastrectomy, as described by Akiyama[5]. In addition to the mediastinal lymph nodes (upper, middle and lower thoracic paraoesophageal lymph nodes, paratracheal lymph nodes, para-aortic thoracic lymph nodes, right and left recurrent nerve lymph nodes, pulmonary hilar and diaphragmatic lymph nodes), the parietal pleura and thoracic duct were resected. The branches of the azygos vein, the pericardium and the opposite pleura were not resected if there was no tumour infiltration (biopsy was performed routinely). Transhiatal resection included resection of the paraoesophageal lymph nodes that could be reached. Abdominal lymph node dissection was performed similarly in both operative procedures with complete dissection of the coeliac lymph nodes between the right gastric artery and splenic hilum. Gastrointestinal continuity was restored by gastric pull-through in 162 patients (94 per cent) or colonic interposition in 11 (6 per cent). After transthoracic resection a high intrathoracic anastomosis was performed in 99 patients (57 per cent) between the oesophagus and the back wall of the stomach using a circular surgical stapler. The cervical anastomosis in 74 patients (43 per cent) was hand sewn.

The median age of the resected patients was 56 (range 29–84) years; 146 (84 per cent) were men. The tumour was located in the upper third of the oesophagus in 16 patients (9 per cent), in the middle third in 71 (41 per cent) and in the distal third in 84 (49 per cent). The pathological tumour node metastasis (pTNM) and R category were assessed according to the Union Internacional Contra la Cancrum (UICC) 1992 classification[6] by an experienced pathologist. Tumour type and differentiation were classified according to World Health Organization criteria[7]. The presence of lymphatic invasion was documented and the removed mediastinal and abdominal lymph nodes were counted carefully. The resection margins (proximal, distal and mediastinal) were marked to estimate clearance.

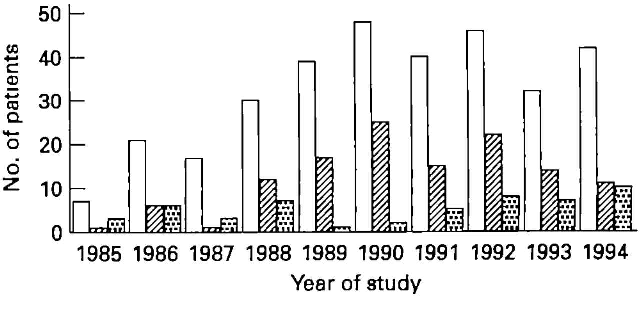

Fig. 1 Distribution of 322 patients with oesophageal carcinoma (□) in the years 1985–1994, and treatment of 173 patients by transthoracic (▨) ($n = 124$) or transhiatal (□) ($n = 49$) resection

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Paper accepted 14 January 1996

The assessment of radicality after histological investigation revealed a curative (R_0) resection in 121 patients (70 per cent) and a palliative (R_1–R_2) resection in 52 (30 per cent).

A prospective protocol was used to record the surgical and general complication rates as well as the duration of intensive care, 30-day mortality, hospital mortality and survival. The deadline for data collection was December 1994. Follow-up was complete for all 173 patients, with a median of 28 (0–99) months in the 49 survivors (28 per cent).

Univariate and multivariate analysis were performed with the χ^2 test, Fisher's exact test, the Mann–Whitney *U* test, the Kruskal–Wallis test, Cox's proportional hazard model and logistic regression. Survival rates were calculated according to Kaplan and Meier, and are given as observed overall survival including postoperative deaths. Significant differences in survival were determined with the log rank test.

All statistical analyses were performed on a personal computer using Superior Performing Software Systems (SPSS for Windows, version 6.0.1; SPSS, Munich, Germany).

Results

Histological examination revealed squamous cell carcinoma in 106 patients (61 per cent) and adenocarcinoma of the oesophagus in 45 (26 per cent); 22 (13 per cent) of the resected patients had an anaplastic tumour. Forty-eight patients (28 per cent) had a tumour classed as stage pT_{1-2}, whereas 125 (72 per cent) had an advanced tumour of stage pT_{3-4}. In 118 patients (68 per cent) regional lymph nodes were involved (pN_1) and in 48 (28 per cent) the coeliac nodes were involved ($pM_{1\,lym}$) (*Tables 1–3*).

Morbidity

Complications occurred in 81 patients (47 per cent). The general complications were adult respiratory distress syndrome in 13 patients (8 per cent), severe pneumonia in 17 (10 per cent), psychosis in nine (5 per cent), heart failure in six (3 per cent), pulmonary embolism in three (2 per cent) and myocardial infarction in two (one per cent). The surgical complications were paralysis of both recurrent nerves in 15 patients (9 per cent), anastomotic

Table 2 Histopathological findings of oesophagectomy specimens removed by transthoracic or transhiatal resection

	Total ($n = 173$)	Transthoracic resection ($n = 124$)	Transhiatal resection ($n = 49$)	*P*
Lymphatic invasion				
No	133 (77)	89 (72)	44 (90)	0·01†
Yes	40 (23)	35 (28)	5 (10)	
Tumour grade				
G_1	3 (2)	2 (2)	1 (2)	0·95*
G_2	63 (36)	44 (35)	19 (39)	
G_3	79 (46)	61 (49)	18 (37)	
G_4	23 (13)	14 (11)	9 (18)	
Not known	5 (3)	3 (2)	2 (4)	
Tumour histology				
Squamous cell carcinoma	106 (61)	80 (65)	26 (53)	0·12*
Adenocarcinoma	45 (26)	31 (25)	14 (29)	
Dedifferentiated	22 (13)	13 (10)	9 (18)	
pT category				
pT_1	22 (13)	13 (10)	9 (18)	0·01*
pT_2	26 (15)	16 (13)	10 (20)	
pT_3	104 (60)	76 (61)	28 (57)	
pT_4	21 (12)	19 (15)	2 (4)	
pN category				
pN_0	47 (27)	28 (23)	19 (39)	0·02†
pN_1	118 (68)	92 (74)	26 (53)	
Not known	8 (5)	4 (3)	4 (8)	
pM category				
pM_0	117 (68)	82 (66)	35 (71)	0·51*
pM_{lym}	48 (28)	36 (29)	12 (24)	
pM_1	8 (5)	6 (5)	2 (4)	
UICC stage				
I	16 (9)	9 (7)	7 (14)	0·10*
IIa	24 (14)	15 (12)	9 (18)	
IIb	13 (8)	8 (6)	5 (10)	
III	64 (37)	50 (40)	14 (29)	
IV	56 (32)	42 (34)	14 (29)	

pTNM, pathological tumour node metastasis; UICC, Union Internacional Contra la Cancrum. *Mann–Whitney *U* test; †χ^2 and Fisher's exact test

Table 1 Details of patients who had oesophagectomy by transthoracic or transhiatal resection

	Total ($n = 173$)	Transthoracic resection ($n = 124$)	Transhiatal resection ($n = 49$)	*P*
Median (range) age (years)	56 (29–84)	55 (29–84)	60 (39–79)	0·02*
Sex ratio (M:F)	146:27	107:17	39:10	0·27†
ASA classification				
I	1 (1)	1 (1)	0 (0)	0 02*
II	51 (29)	41 (33)	10 (20)	
III	102 (59)	73 (59)	29 (59)	
IV	12 (7)	5 (4)	7 (14)	
Not known	7 (4)	4 (3)	3 (6)	
Operation				
Curative	121 (70)	83 (67)	38 (78)	0·35†
Palliative	52 (30)	41 (33)	11 (22)	
Tumour localization				
Upper third	16 (92)	12 (10)	4 (8)	0·05*
Middle third	71 (41)	57 (46)	14 (29)	
Lower third	84 (49)	54 (44)	30 (61)	
Not known	2 (1)	1 (1)	1 (2)	
Median (range) tumour length (cm)	4·0 (0·5–16·0)	4·0 (0·5–16·0)	3·8 (0·7–11 5)	0·66*

ASA, American Society of Anesthesiologists. *Mann–Whitney *U* test; †χ^2 and Fisher's exact test

Table 3 Lymph node dissection, morbidity, mortality and 5-year survival after oesophagectomy by transthoracic or transhiatal resection

	Total ($n=173$)	Trans-thoracic resection ($n=124$)	Transhiatal resection ($n=49$)	P
No. of lymph nodes dissected*				
Total	19·0 (0–94)	24·0 (0–94)	10·0 (0–27)	<0·001†
Abdominal	8·0 (0–51)	8·0 (0–51)	8·0 (0–24)	0·15†
Mediastinal	10·0 (0–83)	15·0 (0–83)	2·0 (0–26)	<0·001†
Invaded	2·0 (0–76)	3·0 (0–76)	1·0 (0–14)	0·008†
Time in intensive care (days)*	10·0 (1–176)	10·0 (1–176)	10·0 (2–68)	0·29†
Overall morbidity	81 (47)	63 (51)	18 (37)	0·10‡
30-day mortality	13 (8)	10 (8)	3 (6)	0·66‡
Hospital mortality	22 (13)	18 (15)	4 (8)	0·26‡
Actuarial 5-year survival rate	13 (16)	13 (21)	0 (0)	0·65§

*Values are median (range) †Mann–Whitney U test, ‡χ^2 and Fisher's exact test; §log rank test

Table 4 Significant variables by multivariate analysis logistic regression for morbidity

Variable	Regression coefficient (β)	Standard error	Risk ratio (e^{β})	P
pT category				
pT_{1-2} *versus* pT_4	−1·26	0·33	0·28	<0·001
pT_3 *versus* pT_4	−0·01	0·28	0·99	
Patient age (years)				
≤60 *versus* >60	−0·40	0·19	0·67	0·04
Tumour localization				
Distal third *versus* proximal and middle third	−0·48	0·19	0·62	0·01
ASA classification				
I–II *versus* III–IV	−0·39	0·19	0·67	0·04

The seven independent variables analysed were patient age, tumour length, operative method, pathological tumour (pT) category, American Society of Anesthesiologists (ASA) classification, tumour localization and number of removed mediastinal lymph nodes

leakage in 13 (8 per cent), wound infection in eight (5 per cent), chylothorax or serothorax in seven (4 per cent), perioperative bleeding in three (2 per cent), interposition necrosis in one (1 per cent) and tracheo-oesophageal fistula in one (1 per cent).

The overall morbidity rate after transthoracic resection was not significantly different from that following transhiatal resection (51 *versus* 37 per cent respectively). The logistic regression analysis included seven variables and identified as independent factors for morbidity the pT category, patient age, American Society of Anesthesiologists (ASA) classification and tumour localization (*Table 4*).

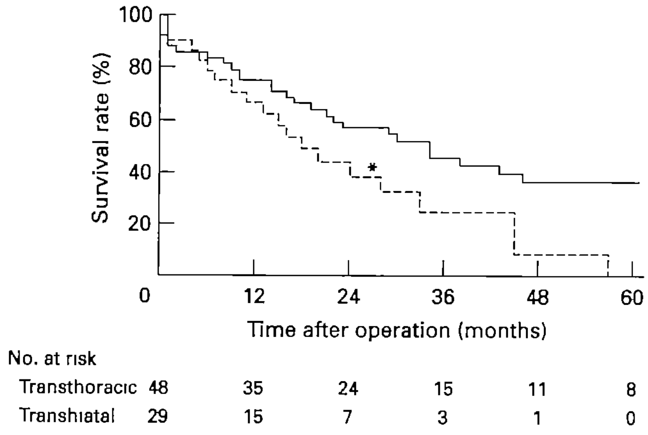


Fig. 1 Distribution of 322 patients with oesophageal carcinoma (□) in the years 1985–1994, and treatment of 173 patients by transthoracic (▨) ($n=124$) or transhiatal (□) ($n=49$) resection

Mortality

The 30-day mortality rate was low after both operative procedures. Ten patients (8 per cent) died after transthoracic resection and three (6 per cent) after transhiatal resection.

Hospital mortality rate after the transthoracic approach was 15 per cent (18 patients) but there was no significant difference compared with transhiatal resection ($P=0·26$). In univariate analysis the tumour length and pT category showed a significant effect on hospital mortality ($P=0·005$ and $P=0·04$ respectively). In addition there was a tendency towards higher mortality in patients with nodal invasion (pN_1), in those classified higher than ASA II and with increasing extent of mediastinal lymph node dissection. Regression analysis was not possible because of the small number of events (22 in 173 patients).

Prognosis

The actuarial 5-year survival rate of all 173 resected patients was 16 per cent, including postoperative hospital mortality. The 5-year survival rates were higher for all UICC stages after the transthoracic procedure. In 77 patients with tumour stage $pT_{1-3}\,pN_{0-1}\,pM_0$, median survival after transthoracic resection was significantly higher than that after transhiatal resection (34(8·3) *versus* 18(3·7) months, $P=0·03$) (*Fig. 2*).

Multivariate analysis of ten variables (Cox proportional hazard model) identified pT category, pM category, lymphatic invasion, operative method and curative resection as independent prognostic factors (*Table 5*).

Lymph node dissection

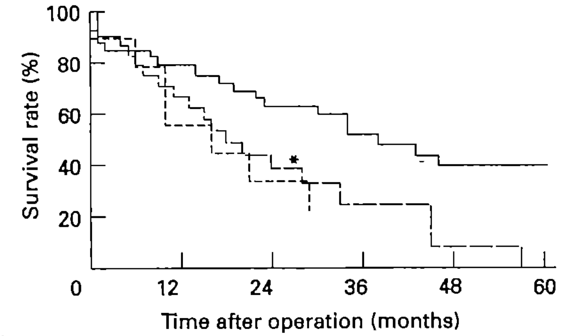
The number of examined abdominal lymph nodes was similar after both operative procedures ($P=0·15$), whereas the number of examined mediastinal lymph nodes was much higher after transthoracic resection with a two-field lymph node dissection. To clarify the importance of mediastinal lymph node dissection total survival was investigated separately in 77 patients without distant metastasis or tumour infiltration of adjacent structures ($pT_{1-3}\,pN_{0-1}\,pM_0$).

In this subgroup, transhiatal resection (group 1, $n=29$)

Table 5 Significant variables by multivariate analysis: Cox proportional hazard model for survival

Variable	Regression coefficient (β)	Standard error	Risk ratio (e^β)	P
pT category				
pT_{1-2} *versus* pT_3	−1·36	0·15	0·87	<0·001
pT_{1-2} *versus* pT_4	1·17	0·22	3·22	
pM category				
pM_0 *versus* pM_{1lym}	0·39	0·10	1·49	<0·001
Curativity				
R_0 *versus* R_1–R_2	0·22	0·11	1·25	0·04
Lymphatic invasion				
Negative *versus* positive	0·26	0·11	1·30	0·02
Operative method				
Transthoracic *versus* transhiatal	−0·29	0·12	1·34	0·02

The ten independent variables analysed were operative method, lymphatic invasion, curativity, pathological tumour node metastasis (pTNM) categories, American Society of Anesthesiologists classification, patient age, tumour localization and tumour histology



No. at risk	0	12	24	36	48	60
Groups 3 and 4	39	30	21	13	9	8
Group 2	9	5	3	2	2	0
Group 1	29	15	7	3	1	0

Fig. 2 Survival after transthoracic (———) and transhiatal (– – –) resection in 77 patients with limited tumour stage (pT_{1-3} pN_{0-1} M_0). *$P = 0·03$ (log rank test)

was compared with transthoracic resection according to the number of examined mediastinal lymph nodes: group 2, 0–5 (median 2) nodes ($n = 9$); group 3, 6–15 (median 10) nodes ($n = 18$); group 4, 16–67 (median 28) nodes ($n = 21$).

Survival time was similar in groups 1 and 2. On the other hand, the median total survival increased with increasing number of resected mediastinal lymph nodes (group 1, 18(3·7) months; group 2, 16(8·9) months; group 3, 43(10·1) months; group 4, 34(10·1) months). Between groups 3 and 4 there was no additional significant prognostic difference. Patients in groups 3 and 4 together had prolonged survival compared with those having transhiatal resection (median(s.e.m.) 38(7·3) months, $P = 0·01$) (*Fig. 3*).

No significant differences were shown (group 1 *versus* groups 3 and 4) in patient age, length of intensive care, tumour length, ASA classification, sex distribution, tumour localization, tumour grading, pT category, pN category, morbidity and mortality (data not shown).

The 5-year survival rate of patients in groups 3 and 4 was 40 per cent whereas none of those in group 1 is alive 5 years after surgery (*Fig. 3*).

Discussion

Reduction of the operative risk and improvement in prognosis are the goals of every operation and are the decisive criteria in selection of the surgical approach. There is still controversy about the value of local radicality in patients with oesophageal cancer, and especially regarding the importance of mediastinal lymph node dissection. Several authors[1,2,8,9] have recommended the transhiatal procedure because of the reduction in operative risk. Others[3,10–12] have extended lymph node dissection up to the cervical field and report a better prognosis. Bonavina[4] also showed a higher 5-year survival rate in patients with submucosal oesophageal cancer after transthoracic resection compared with transhiatal oesophagectomy; however, he did not describe the quality of the lymph node dissection. Horstmann *et al.*[13] reported similar low survival rates for both operative procedures (21 and 17 per cent after 3 years), but they did not state the number of mediastinal and abdominal lymph nodes examined.

In the present authors' institution the procedure of choice for patients with oesophageal cancer is abdominothoracic *en bloc* resection, mediastinal lymph node dissection and restoration of gastrointestinal continuity by gastric pull-through. In high-risk patients, however, the transhiatal approach is preferred if this is practicable. During the period under consideration, one-quarter of the patients had transhiatal resection and three-quarters had a transthoracic approach with progressive extension of the mediastinal lymph node dissection with time. The aim of the prospective follow-up was to identify situations in which mediastinal lymph node dissection is useful and necessary, and those in which it is without benefit. Because a randomized study is not possible on ethical grounds, this study was performed by comparing prospectively collected data.

Because of the different indications for operation, morbidity and mortality are not comparable between the two approaches. The transhiatal resection was performed in patients with limited functional reserve and with limited tumour size. Seventy-eight per cent of these patients were in the ASA group III–IV (compared with 65 per cent of those who had transthoracic resection). However, the postoperative morbidity and mortality rates, as well as the duration of intensive care, were lower following transhiatal resection. On the other hand, patients in the transthoracic group had large tumours which more frequently could not be resected for cure. This explains the higher morbidity and mortality rates after this approach. In regression analysis only tumour and patient factors (pT_4 category, proximal and middle third tumour location, age over 60 years and ASA grade over II) were identified as independent factors for morbidity.

The prognostic factors tested were, first, tumour-related factors such as pT category, invasion of coeliac lymph nodes (pM_l) and lymphatic invasion, and, second, surgical factors like curativity and choice of operative method. In this analysis the surgical factors were of particular importance in 103 patients (60 per cent) with limited tumour stage (pT_{1-3} pN_{0-1} pM_0). The curatively resected patients of this group ($n = 77$) were therefore analysed with special emphasis on mediastinal lymph node dissection (groups 1–4).

Comparison of the prognosis of two operative methods with different radicality is always difficult because of staging factors; the N_0 patient group may incorrectly include some patients with metastases in the transhiatal group. Nevertheless, in ten of 15 patients in group 1 classified as pN_0 after transhiatal resection, the number of examined tumour-free lymph nodes (abdominal and mediastinal) was over ten. Seven of these patients were classified as stage N_0 by endosonography before resection and are still alive.

Despite this methodological difficulty, mediastinal lymph node dissection in transthoracic resection (groups 3 and 4) was associated with longer survival than transhiatal resection (group 1) or transthoracic resection without lymph node dissection (group 2).

These results suggest that survival benefit can be achieved in patients suffering from oesophageal cancer if the disease is limited (T_{1-3} N_{0-1} M_0) and curative *en bloc* resection including mediastinal lymph node dissection is performed. In the authors' opinion the reasons for this are a higher number of removed invaded lymph nodes or resection of micrometastases in apparently uninvolved lymph nodes.

Akiyama *et al.*[3] reported a clear benefit in patients with additional cervical lymph node dissection (three fields). Baba *et al.*[10] and Lerut and co-workers[11] have also emphasized the value of three-field lymph node dissection. However, their 5-year survival rate for patients with UICC stage I and II disease, and overall 5-year survival rate after curative transthoracic resection with two-field lymph node dissection, are similar to those reported here.

Survival was independent of mediastinal lymph node dissection in patients with an advanced oesophageal tumour (pT_4) or following resection of distant metastasis (liver, lung); palliative procedures are feasible in these situations. If the coeliac lymph nodes were invaded, survival decreased remarkably. There were few such cases and no distinction could be made between the two operative methods in this situation.

The results of this study suggest that selection of the operative approach may be based on the following criteria: (1) if preoperative staging by endosonography suggests UICC stage 0, the transhiatal approach might be regarded as appropriate; (2) in patients with advanced disease (pT_4, pM_1) the transhiatal approach is appropriate because of lower operative risk and unimprovable prognosis; and (3) in patients with limited tumour stage (pT_{1-3} pN_{0-1} pM_0) the abdominothoracic route with routine two- or three-field lymph node dissection should be chosen.

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Erratum

M. K. Roy, M. Rhodes, M. S. T. Ruttley and M. H. Wheeler. Sengstaken tube for bleeding rectal angiodysplasia. *British Journal of Surgery* 1996; **83**: 1111.

Fig. 1 was published incorrectly rotated clockwise at a 90° angle. The Journal apologizes to authors and readers.

British Journal of Surgery 1996, 83, 1478–1484

Correspondence

Mechanism for port-site metastasis after laparoscopic cancer surgery

Sir

We read with great interest the recent correspondence concerning the, as yet elusive, mechanism responsible for port-site tumour recurrence (*Br J Surg* 1986; 83. 133). Messrs Taffinder and Champault believe that airborne exfoliated tumour cells carried in the carbon dioxide leaking around the trocars, the so-called 'chimney effect'[1], may become trapped in the port wound surfaces, resulting in parietal recurrences. They should be congratulated on their success in isolating clumps of whole cells in the smoke aspirated during laparoscopic procedures; they have certainly made a good start. Still there is a long way to go: they have to prove the occurrence of three further events First, tumour cells have to be demonstrated in the smoke. Second, the tumour cells in aerosol form have to be shown to settle on the wound surfaces. Third, the implanted cells must be seen subsequently to grow into tumour nodules.

The authors revealed their plan to biopsy trocar sites to confirm tumour implantation In our hospital we have been examining biopsies diligently from all port sites following laparoscopic resection of colonic cancers and following resection of clinically evident port-site recurrences. To our surprise, in the case of a 61-year-old man with carcinoma of sigmoid colon, we found clumps of tumour cells with histological features of the primary growth in biopsies of both the camera and the right port wounds (*Fig 1*) We believe we are the first to provide hard evidence of tumour implantation.

Trocar site recurrence cannot be solely attributed to direct contact of the port wound with tumour-laden instruments. There have been reports of tumour recurrences occurring almost simultaneously in all ports, including the camera port which had not contacted either the cancerous specimen or the laparoscopic instruments[2–4]. Furthermore, in our studies on trocar biopsy, fragments of tumour tissue were seen buried deep in the abdominal wall muscle fibres. It looked as though they had been forcibly pressed into the muscle tissue (possibly propelled by the jet of carbon dioxide under pressure) However, the 'chimney effect' hypothesis cannot explain the development of malignant implants in chest wounds after thoracoscopic surgery in which carbon dioxide pneumoperitoneum was not used[5,6].

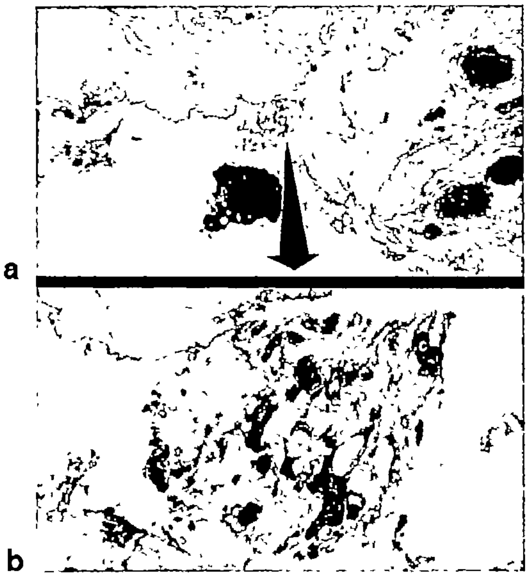

Fig. 1 a A clump of tumour cells is seen in the middle of tissues of the camera port biopsy (haematoxylin and eosin, original magnification ×40). b Magnified view of the clump of mucinous adenocarcinoma cells (haematoxylin and eosin, original magnification ×250)

Another possible mechanism is that, after deflation, the abdominal wall sags down, allowing the exfoliated tumour cells in the peritoneal fluid to be implanted into the undersurface of the port wound where the mesothelial cells are damaged or missing. While this mechanism might lead to parietal metastases extending from the peritoneal surface, it cannot account for recurrences localized only in the superficial subcutaneous fat (as in one of our five patients with proven recurrence)[7].

We believe, therefore, that multiple mechanisms are involved in the pathogenesis of port-site recurrence. Further basic scientific studies are necessary to unveil the whole mystery of this phenomenon.

W. T. Ng
H. C. Yeung
G. H. Koh
W. F. Ng

Departments of Surgery and Pathology
Yan Chai Hospital
Yan Chai Street
Hong Kong

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Typhoid enteric perforation

Sir

I read with interest the study by Dr Akgun and colleagues (*Br J Surg* 1995; 82. 1512–15) on the management of typhoid enteric perforation and I congratulate them on collecting such a large series. Although I agree with many of their recommendations for the treatment of this difficult problem, I would like to point out that the conclusions they have drawn from their study are not supported by the data given. They have clearly demonstrated the direct relationship between mortality rate and the time interval from perforation to operation in their retrospective group (*Fig. 2* of article). We have demonstrated a similar relationship in a restrospective review over 5 years from July 1988 to June 1993 at our institution. We operated on 26 patients with typhoid enteric perforation: there were no deaths in patients with a perforation-to-operation interval of less than 48 h, one death in four patients with a history of 48–120 h, and four deaths in nine with a history of over 120 h. Perforation-to-operation interval is the single most important prognostic factor in patients wtih typhoid enteric perforation.

Although the authors state that the prospective group 'was not different from the retrospective series in any of the prognostic indices of age distribution, clinical signs and symptoms or laboratory findings', there is a clear difference between the two groups with respect to perforation-to-operation interval. They state that, in the retrospective group, only 65 (24 per cent) of 267 were admitted within 48 h of perforation and that this group had a mortality rate of 9·2 per cent. The vast majority of the retrospective group (76 per cent) was admitted after 48 h. In the prospective group 'the median interval between perforation and operation was 46 h', and there were four deaths in 34 patients. There were no patients with a history of over 5 days in the prospective group

From these data it is not justified to attribute the improvement in the outcome after typhoid enteric perforation to the changes made in their management. The overall improvement in mortality rate after operation could equally be explained by the earlier presentation of patients in the prospectively assessed group. To advocate 7 days of total parenteral nutrition (TPN) for a condition that primarily occurs in the world's poorest countries on the basis of this study may have the unfortunate consequence of diverting valuable resources away from more essential treatments to pay for TPN. I would certainly agree that aggressive preoperative fluid and electrolyte resuscitation is essential, and that antibiotics appropriate to local *Salmonella typhi* sensitivity and also covering anaerobic bacteria should be utilized. Our regimen involves vigorous fluid resuscitation using Ringer's lactate solution and antibiotic treatment with metronidazole and ciprofloxacin (80 per cent of local *S. typhi* strains are resistant to chloramphenicol)[1] In patients presenting less than 5 days after perforation (a group comparable to the prospective group in their study), we had only one death in 17 patients, which compares favourably with their results.

In summary, the study by Dr Akgun, although impressive in size, may be misleading because it fails to recognize the confounding effect of perforation-to-operation interval between the two groups. Similar results can be achieved in situations where TPN is not available provided the basic principles of adequate preoperative resuscitation and antibiotic treatment are practised

I. P. Bissett

Department of Surgery
Western Regional Hospital
Pokhara
Nepal

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Author's reply

Sir
I am pleased that our article has been of interest, and I am glad to be able to discuss the suggestion of Dr Bissett

There was a negative nitrogen balance in all patients because of septicaemia, and the median hospital prognostic index was 0·920. On the basis of these findings, total parenteral nutrition (TPN) was initiated in the early postoperative period. TPN may be expensive but does not cost as much as a life, even in the world's poorest countries It is required especially in patients whose hospital prognostic index is less than 1

We did not perform culture and sensitivity tests, but found that the combination of chloramphenicol, ampicillin/sulbactam and ornidazole was effective. Since 1993 we have also used ciprofloxacin and chloramphenicol at random in the treatment of typhoid enteric perforation. At present, we have not found any statistical differences between ciprofloxacin and chloramphenicol, though this study is still ongoing.

In a prospective study, four patients who died had been admitted to hospital in septic shock, and their perforation-to-operation interval was more than 3 (median 4) days.

Y. Akgun

Dicle Universitesi Tip Fakultesi
Genel Cerrahi Anabilim Dali
21 280 Diyarbakir
Turkey

Ultrasonographic carotid plaque morphology in predicting stroke risk

Sir
Each time we open a carotid artery containing soft haemorrhagic plaque, common sense tells us that this friable tissue must be a source of distal embolization and consequently a source for the cerebral symptoms encountered by our patients. We therefore find it relatively easy to be persuaded by the powerful arguments advanced for the role of haemorrhagic plaque in the development of cerebral symptoms put forward by Dr Geroulakos and colleagues (*Br J Surg* 1996; **83**: 582–7). However, the role of plaque type in the development of cerebral symptoms may be considerably more complex than the simple view that soft pieces of haemorrhagic material are becoming dislodged. There were some surprising findings in our own study of the role of carotid plaque morphology in the development of symptoms[1] based on a series of 4258 carotid arteries of all degrees of stenosis, 1342 of which were symptomatic and 1558 of which were identified as having characterizable plaque. We found that the two parameters of plaque morphology and degree of stenosis were very closely related and almost inseparable Thus at under 20 per cent stenosis 96 per cent of plaques were fibrous, whereas at more than 80 per cent stenosis 85 per cent of plaques were haemorrhagic. In addition, although type I haemorrhagic plaques are associated with more symptomatic vessels, it is impossible to attribute this finding simply to plaque type because all these vessels have a high degree of stenosis. It was our conclusion that plaque morphology did not add to the sensitivity of degree of stenosis in predicting the presence of symptoms

We also demonstrated that the only symptom that may be more likely to be associated with haemorrhagic plaque is amaurosis fugax. Therefore, studies of symptomatic patients that contain large numbers of patients with amaurosis fugax may be biased to finding more with type I plaque. The conclusions from these studies cannot therefore be translated to symptoms of other conditions such as transient ischaemic attacks or strokes.

In a further study (currently undergoing peer review), we have also shown that type I haemorrhagic plaque is three times more likely to be found in men. However, once again we did not find that this was translated into an increase in symptoms in men As the degree of carotid stenosis increases, so the type of plaque changes to a more haemorrhagic form This fact may well be the result of altered flow dynamics within the vessel creating shear stresses as a result of the Bernoulli effect[2] rather than any intrinsic change within the composition of the atheroma.

Although we would like to believe that soft haemorrhagic plaque is a marker for patients at high risk of stroke, we consider that it is no more than a marker of increased severity of generalized atherosclerosis, and as an indirect result will inevitably be associated with a higher number of strokes. This suggestion is illustrated by the fact that those with high-risk plaques are more likely to have a myocardial infarction or problems with peripheral vascular disease than they are to have cerebral ischaemic events[3].

We would agree with Dr Geroulakos and colleagues that the criteria for selection of high-risk patients for carotid surgery should be better defined. However, it is idealistic to believe that this can be achieved by looking simply at either the degree of stenosis or the plaque morphology in the internal carotid artery Working on the basis that at least two-thirds of patients with strokes have normal carotid arteries, we should assume that a much more complex series of physiological events is taking place leading to cerebral ischaemia.

R. J. Holdsworth
P. T. McCollum

Department of Vascular Surgery
Dundee Teaching Hospitals NHS Trust
Ninewells Hospital and Medical School
Dundee DD1 9SY
UK

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Screening for colorectal cancer with an immunological faecal occult blood test: 2-year follow-up

Sir

Dr Robinson and colleagues (*Br J Surg* 1996; **83**: 500–1) suggest that faecal occult blood screening can be improved, but screening with guaiac-based tests has some potential shortcomings[1]. Although the benefit and effectiveness of such screening remains controversial, the mortality rate from colorectal cancer necessitates the revision of current policies and the development and introduction of new methods and markers.

Although more sensitive and human-specific immunological methods have been developed in recent years, these techniques are usually limited to the demonstration of haemoglobin in the faeces[2]. This practice has several inherent difficulties due to the degradation of haemoglobin and the irreversible binding of its major constituent to a special component of the faeces. Recently, some authors have proposed the parallel study of other blood proteins as well[3,4], since they are more stable in faeces than haemoglobin We wished to examine the potential advantages of parallel analysis of haemoglobin and albumin in faecal samples from young, healthy subjects and patients with verified colorectal carcinoma[5]. Our experiments showed that the parallel demonstration of the two proteins significantly enhanced the detectability of colorectal cancer. Therefore, further studies to demonstrate the efficacy of the method were carried out with screening of symptom-free individuals. The method does not require any dietary modification.

Our screening population included 4223 persons selected randomly with an approximately even proportion of both sexes. Mean age was 55 years The positivity ratio was 4·5 per cent and only those patients were referred for endoscopy. Colonic or rectal carcinoma was detected in nine patients (Dukes stage A, two; B, six; C, one) The youngest patient was a 39-year-old woman and the oldest an 80-year-old man. With the aid of antihuman haemoglobin immune serum alone, we could have detected only six carcinomas and overlooked three (Dukes stage A, one, B, two).

We are sure that the current form of mass faecal occult blood screening is indispensable, but its conditions should be modified. Naturally, efforts should be made to search for new and more potent biochemical and genetic markers and to test them in clinical practice.

S. Otto
M. Németh

National Institute of Oncology
H-1525 Budapest
PO Box 21
Hungary

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Immune function early in acute pancreatitis

Sir

Messrs Widdison and Cunningham (*Br J Surg* 1996; **83**: 633–6) drew attention to lymphopenia in pancreatitis and suggested that it might be because of redistribution of lymphocytes from blood to other tissues rather than impaired immune function. Soo *et al.*[1] have provided evidence for this in patients with acute apendicitis. Their patients showed: (1) lymphopenia especially with severe sepsis; (2) CD4/CD8 ratios unchanged; (3) depletion of T cells affecting memory cells of phenotype CD45R0 while leaving in circulation naive cells of CD45RA phenotype, (4) accumulation of memory cells in the inflamed appendix; and (5) migration of memory cells from blood to appendix proved by sampling blood from both appendicular artery and vein. The T cells remaining in the blood were less reactive in proliferation assays than those in the inflamed (but not the normal) appendix. Selective cellular migration may thus explain the anergy of peripheral blood lymphocytes from septic patients.

Similar changes may occur in pancreatitis and other surgical disasters in which lymphopenia was described as long ago as 1952[2].

We have examined blood counts for all patients admitted under a general surgical service over 1 year in the hope of gaining some understanding of the pathology leading to lymphopenia (*Table 1*). If we are to postulate that sepsis was the sole or main determinant of lymphopenia, we shall have to accept that both pancreatitis and bowel obstruction presented a septic challenge. And what of 'assorted abscesses'? Were they too small to have an effect, or were they infected with the wrong sorts of bacteria? We agree with Messrs Widdison and

Table 1 Data for 644 patients who underwent general surgery

Diagnosis	No. of patients	Mean lymphocyte count* (× 10⁹/l)	95 per cent confidence interval
Hernia (elective operation)	109	1·83	1·63–2·03
Benign breast disease	20	1·71	1·50–1·92
Breast cancer	36	1·70	1·54–1·85
Assorted abscesses	36	1·70	1·30–2·10
Varicose veins	46	1·60	1·46–1·75
Bleeding (mainly gastrointestinal)	31	1·59	0·76–2·42
Gallstones	28	1·54	1·21–1·87
Abdominal pain (non-specific)	88	1·45	1·27–1·62
Peripheral vascular disease	70	1·37	1·20–1·53
Appendicitis	63	1·24	1·10–1·38
Pancreatitis	26	1·03	0·68–1·38
Acute cholecystitis	18	0·99	0·60–1·38
Diverticulitis	15	0·90	0·59–1·22
Bowel obstruction	38	0·80	0·67–0·92
Bowel perforation	20	0·59	0·47–0·71

*Performed on Technicon H-1 Analyser (Bayer Diagnostics, Newbury, UK). For each patient with more than one blood count, the lowest preoperative lymphocyte count was taken. Other arbitrary selection criteria produce a similar pattern of results

Cunningham that further studies are needed to investigate lymphocyte kinetics and function in surgical patients.

J. H. Wyllie
F. Myint

Department of Surgery
Whittington Hospital
London N19 5NF
UK

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'Residual' appendicitis following incomplete laparoscopic appendicectomy

Sir
With reference to the recent article by Messrs Milne and Bradbury (*Br J Surg* 1996; 83: 217) and the letter by Messrs Somerville and Lavelle (*Br J Surg* 1996; 83: 869) concerning incomplete removal of the appendix laparoscopically, we agree that recurrent appendicitis after appendicectomy is not peculiar to the laparoscopic approach. We are aware of a case of 'recurrent appendicitis' 10 years after open appendicectomy. A 32-year-old woman presented with clinical signs of infection and a painful induration around a 10-cm long old appendicectomy scar. At laparotomy, we found a growth of inflammatory and granulation tissue through the abdominal wall between caecum and the subcutaneous layer An ileocaecal resection was performed and the postoperative course was uneventful[1]. As the histological examination confirmed our suspicion, we believe that the appendicectomy 10 years previously did not remove the organ as completely as it should have.

Especially, but not exclusively, in the laparoscopic era we would like to emphasize the importance of careful identification of the appendix base and complete resection. A 'recurrent appendicitis' may occur after a short time, or very late after the first surgical procedure, as in our patient.

N. Demartines
J. Largiadèr

Department of Surgery
Kantonsspital of Lucerne
CH 6000 Luzern 16
Switzerland

1 Demartines N, Largiadèr J. 'Recidive' d'appendicite 10 ans après appendicectomie. *Lyon Chir* (in press).

No obvious advantages for thoracoscopic two-stage oesophagectomy

Sir
I was interested to read the article by Mr Robertson and colleagues on the advantages and disadvantages of thoracoscopic oesophagectomy (*Br J Surg* 1996; 83: 675–8), but regret that they perpetuate the error of attributing the one-stage combined abdominal and right thoracic approach oesophagectomy solely to Ivor Lewis (not Ivor–Lewis (*sic*) as in their article). Lewis originally described an oesophagectomy in two stages, separated by an interval[1]. An initial laparotomy was performed preparing the stomach for subsequent repositioning and anastomosis in the chest 2 weeks later via a right thoracotomy. Norman Tanner independently originated a similar procedure, but in one stage[2], in the same year (1944) that Lewis initiated the two-stage operation. Tanner's publication, however, appeared 9 months after Ivor Lewis's contribution was published in this journal.

Incidentally, Norman Tanner was a good friend of Ivor Lewis and while I was Tanner's Registrar at St James, Balham, London in 1958, he performed a Billroth I gastrectomy on his friend for a benign gastric ulcer.

As the Tanner one-stage procedure is that which is in common use today, it would seem appropriate that the names of both these outstanding British surgeons be linked to the operation they independently pioneered, the Lewis–Tanner oesophagectomy.

R. Britten-Jones

Department of Surgery
University of Adelaide
Royal Adelaide Hospital
Adelaide 5000
South Australia
Australia

1 Lewis I. The surgical treatment of carcinoma of the oesophagus with special reference to a new operation for growths of the middle third. *Br J Surg* 1946; 34: 18–31.
2 Tanner NC. Carcinoma of the oesophagus. *Postgrad Med J* 1947; 23: 109–39.

Colonic decompression without on-table irrigation for obstructing left-sided colorectal tumours

Sir
We read with interest the article by Mr Nyam and colleagues concerning the intraoperative decompression of the obstructed left colon (*Br J Surg* 1996; 83: 786–7) and are in agreement that on-table colonic lavage is unnecessary in some instances. We have found that milking the bowel contents into the specimen before resection further reduces operating time and the risk of peritoneal contamination, and we would advocate this as a technique.

A. W. Lambert
C. Ranobaldo

Royal United Hospital
Combe Park
Bath BA1 3NG
UK

Thrombolysis for acute deep vein thrombosis

Sir
We enjoyed the paper by Armon and Hopkinson (*Br J Surg* 1996; 83: 580–1) on thrombolysis for deep vein thrombosis (DVT) and agree that this modality of treatment needs to be investigated further, and its effectiveness in preventing pulmonary embolism and chronic venous insufficiency needs to be established. We also agree that there needs to be strict selection criteria for patients receiving this treatment. Our comments relate to below-knee DVT which we believe merits different management.

Armon and Hopkinson suggest that untreated below-knee DVT results in a 30 per cent incidence of pulmonary embolism and that 20–40 per cent of these will be fatal (i.e. 6–12 per cent of patients with below-knee DVT will die from pulmonary embolism). Although there is a high incidence of episodes of silent pulmonary embolism in both above- and below-knee thromboses, anticoagulant therapy does not seem to affect the incidence of pulmonary embolism in patients with below-knee DVT[1]. Furthermore, clinically significant pulmonary embolism occurs only when the thrombus progresses proximally[2]. In a study on 90 patients who underwent screening duplex scans after operation, distal DVT was detected in ten patients (9·1 per cent). None of these (followed for 14 days with daily scans) manifested either symptomatic DVT or pulmonary embolism. The follow-up extended to 12 months[3]. In another study no demonstrable effect on progression of below-knee DVT in mobile patients wearing thrombo-embolic deterrent stockings (TEDS) and treated with phenylbutazone was seen compared with those wearing TEDS and treated with anticoagulant therapy[4]. Finally, thrombolysis is not without danger. Complications of internal and external bleeding, as well as the possibility of sending fresh showers of pulmonary emboli, must not be ignored.

We consider that below-knee DVT should be managed by serial duplex scanning and antiplatelet medication[3]. If proximal progression of thrombus is detected, the patient is treated with full anticoagulation. We also believe that, in studies on thrombolytic therapy in acute DVT, patients with below-knee DVT should be excluded.

S. S. Shoab
S. K. Shami

Vascular Unit
Havering Hospitals
Oldchurch Hospital
Waterloo Road
Romford RM7 0BE
UK

1 Nielson HK, Husted SE, Krussell LR *et al.* Silent pulmonary embolism in patients with DVT. Incidence and fate in a randomized controlled trial of anti-coagulation *versus* no anti-coagulation. *J Intern Med* 1994; 235: 457–61.
2 Creager MA, Dzau VJ. Vascular diseases of the extremities. In Wilson JD, Braunswald EB, Petersdorf RG, Martin JB, Fauci AS, Root RK, eds. *Harrison's Principles of Internal Medicine.* New York: McGraw Hill, 1991: 1024.
3 Grady Benson JC, Oishi CS, Hanson PB *et al.* Routine post-operative duplex ultrasonography screening and monitoring for the detection of DVT. Survey of 110 total hip arthroplasties. *Clin Orthop* 1994; 307; 130–41.
4 Nielson HK, Husted SE, Krussell LR *et al.* Anticoagulant therapy in DVT, a randomized controlled study. *Thromb Res* 1994; 73: 215–26.

Authors' reply

Sir

We are grateful for the comments of Messrs Shoab and Shami. At the risk of deflecting attention away from the bulk of our article by dealing with matters relating to the introductory paragraph, we would like to respond

We accept that the risk of pulmonary embolism from below-knee deep vein thrombosis (DVT) is small, when treated. However, untreated below-knee DVT can progress and the patient may therefore run the risk of fatal pulmonary embolism. Untreated pulmonary embolism has a high associated mortality rate and it is for this reason that we have quoted a figure of 20–40 per cent based on the work of Schulman[1] This is, of course, a difficult figure to prove or disprove due to ethical constraints. The only randomized study of no treatment *versus* heparin for pulmonary embolism in 1960 was stopped after five of 19 patients in the untreated group died from fatal pulmonary embolism[2]. Nielson's trial in the two papers cited compares two treatment options rather than anticoagulation *versus* no treatment.

We wish to emphasize that the main reason for advocating thrombolysis as a treatment option for acute DVT is not to prevent pulmonary embolism, a job done admirably by anticoagulation, but to prevent the post-thrombotic syndrome or chronic venous insufficiency Chrome venous insufficiency undoubtedly does occur following some below-knee DVTs, so we hesitate to rule these patients out entirely as candidates for a treatment that may confer long-term benefit. Only limited conclusions can be drawn from just ten screen-detected DVTs followed for only 12 months in Grady's study. Nevertheless, as stated in our article, we agree that invasive treatment, such as catheter-directed thrombolysis, should be concentrated on patients with more severe proximal DVT, as these patients have most to gain.

M. P. Armon
B. R. Hopkinson

University Hospital
Nottingham NG7 2UH
UK

1 Schulman S. Studies on the medical treatment of deep vein thrombosis. *Acta Med Scand* 1986; 704(Suppl): 1–68
2 Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. *Lancet* 1960; i: 1309–12.

Conversion operation for alkaline reflux after total gastrectomy and Schloffer reconstruction

Letter 1

Sir

We agree with Dr Fass and colleagues (*Br J Surg* 1996, 83: 270–1) that alkaline reflux can often complicate a loop oesophagojejunal anastomosis after total gastrectomy, and were interested to read their technique of conversion to a Roux-en-Y loop. In 1988, we reported a similar method which involves application of a linear stapler (TA55; AutoSuture, Ascot, UK) across the afferent limb of the jejunal loop just above the enteroenterostomy[1]. The procedure is simple to perform and avoids the often difficult dissection under the diaphragm. We have used this technique on several occasions with good results and have recently encountered a patient who bears testament to its efficacy.

A 61-year-old man underwent total gastrectomy for an early gastric cancer with reconstruction by loop oesophagojejunal anastomosis and enteroenterostomy. He initially made an uncomplicated recovery but 1 year later presented with severe biliary reflux, confirmed on endoscopy. He therefore underwent the procedure described with complete resolution of his symptoms. Six months later he developed symptoms of both biliary colic (with gallstones confirmed on ultrasonography) and a recurrence of the biliary reflux. Laparotomy demonstrated not only cholelithiasis but that the staple line across the afferent loop had opened. Cholecystectomy was performed and the afferent limb was reoccluded with a stapling gun. On review 6 weeks later, all symptoms had resolved. We recommend this procedure as a quick, simple and effective alternative to the operation described by Dr Fass and colleagues.

J. A. Grabham
J. M Kelly

Department of Surgery
Queen Alexandra Hospital
Portsmouth PO6 3LY
UK

1 Chiverton SG, Kelly JM. An easy way to convert to loop esophagojejunal anastomosis to Roux-en-Y anastomosis. *Surg Gynecol Obstet* 1988; **166**: 277.

Letter 2

Sir

We read with interest the excellent paper by Dr Fass and colleagues (*Br J Surg* 1996; 83. 270–1). May we comment briefly on a few aspects of this article? The vast majority of patients having so-called alkaline reflux oesophagitis and its consequences have had previous gastric and/or oesophageal operations that permit free flow of duodenal contents back into the oesophagus.

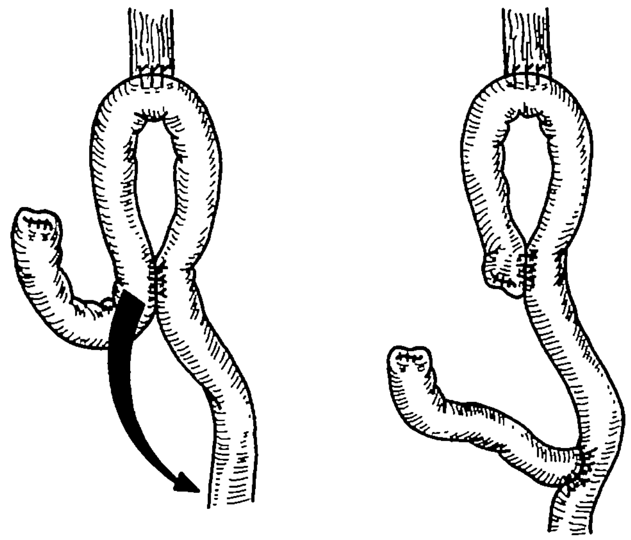

Fig 1 Schematic diagrams showing conversion operation for alkaline reflux after oesophagojejunostomy with entero-enterostomy

This pathological finding could make the life of patients completely unbearable. Adequate drug treatment is presently not available. Most of these patients require remedial surgery. Antireflux surgery with biliary diversion – as mentioned by the authors – has become the treatment of choice There are different possible surgical interventions and that choice should be guided by a complete understanding of the patient's symptoms and investigation of the underlying pathophysiological and anatomical abnormalities.

Until 1994, 35 reoperations were performed because of alkaline reflux oesophagitis in our department. In two cases, after total gastrectomy the operation was a loop oesophagojejunostomy. The solution was to perform a Roux-en-Y formation In six cases the previous operation was a loop oesophagojejunostomy of the Braun type. The enteroanastomosis was not sufficient to divert the duodenal content because of the effect of the isoperistaltic afferent loop. The afferent loop was transected below the level of the enteroenterostomy. So the anastomosis remained functional and an additional end-to-side enterostomy was performed. The length of the loop between the two anastomoses had to be more than 50 cm – as usual (*Fig. 1*) No patient died and the complaints resolved. Different examinations such as radiography, endoscopy and even hepatobiliary scintigraphy showed no pathological conditions.

The advantages of this solution are as follows. (1) Adhesions are frequent in the region of the oesophagojejunal anastomosis If the proposed solution is adopted it is not necessary to operate in this region which can be especially difficult if the anastomosis has been performed in the mediastinal space. (2) It is not necessary to perform a so-called ventral hemijejunoplication; we are not convinced that it has an antireflux effect The authors themselves mentioned that the main factor preventing reflux is a long Roux loop of at least 50 cm and in our opinion this in itself is enough.

J. Kiss
A. Võros
Á Altorjay
I. Rózsa

Department of Surgery
Postgraduate Medical School
Szabolcs u 33. Pb. 112.
Budapest
Hungary
H-1389

Author's reply

Sir

We are very grateful for the great interest in our procedure demonstrated by two such expert letters describing interesting alternative methods of treating alkaline reflux after total gastrectomy and Schloffer reconstruction. Both methods, described by Messrs Grabham and Kelly, and Professor Kiss *et al.*, have in common that they more or less preserve the afferent loop of the previous Schloffer reconstruction. As Professor Kiss correctly mentioned, the isoperistaltic afferent loop of the Schloffer reconstruction is the cause of jejuno-oesophageal reflux, even if there is diversion by an enteroanastomosis. Considering data from the literature, the Roux loop would have to be 50 cm long below the old enteroanastomosis to achieve an effective prevention of ascending duodenal contents. We believe that in such a reconstruction the resorptive capacity of the small bowel would be restricted too much by the gastric substitution. Additionally, in Mr Grabham's procedure, the afferent loop acts as a blind loop. In the case described, this even led to the opening of a staple line We agree with Professor Kiss *et al.* that ventral hemijejunoplication is not mandatory to prevent reflux, but it helps to prevent a blind loop effect and construct a normal Roux-en-Y procedure.

In our experience the preparation of the anastomotic region is not problematic as long as the anastomosis is within the abdominal cavity and there is no history of an insufficiency. During dissection, mobilization of the left lobe of liver is generally an easy way of finding a previously untouched area close to the anastomosis

J. Fass

Department of Surgery
RWTH Aachen
Pauwelsstrasse 30
D-52074 Aachen
Germany

An evaluation of the POSSUM surgical scoring system

Sir

Mr Whiteley and colleagues complain that no details have been reported of how to apply the POSSUM system (*Br J Surg* 1996; 83· 812–15) despite many publications showing its application in surgical research and audit. It would appear, however, that their only concern is that they are unable to calculate the total number of predicted deaths from a group whose individual risks of death are determined from the POSSUM (Physiological and Operative Severity Score for the enUmeration of Morbidity and mortality) predictor equation for mortality Simply calculating mean risk is not a valid method of predicting the total number of deaths. The original POSSUM equations were based on the observed mortality and morbidity rates for all patients with scores above each particular level Therefore a minimum mortality rate of 1·08 per cent assumes that all patients with physiological scores above 12 and/or operative severity scores above 6 will have this overall risk of death. This rate is indeed the one seen worldwide. It should also be remembered that POSSUM is an audit aid and, as such, is not intended to be a perfect predictor of death or complication for an individual patient, but for a patient group.

Whiteley *et al.* also state that their sample was representative of the general surgical workload However, just over 5 per cent of their sample had a greater than 25 per cent risk of death. It only requires an elderly patient with an abnormal electrocardiogram to undergo elective surgery for intra-abdominal malignancy to provide a greater than 25 per cent mortality risk. This fact means that either the population of Portsmouth is very fit, they undergo only minor surgery, or, as is more likely, the sample was not representative and length of stay is not 'indicative of both the severity of the operation performed and the physiological state of the patient'. All non-day-case surgical patients should be included but they have not stated whether or not all emergency surgical procedures were included.

B. S. McIlroy
G. P. Copeland*

Departments of Surgery
Withington Hospital
Nell Lane
West Didsbury
Manchester M20 8LR
and
**Warrington Hospital*
Lovely Lane
Warrington WA5 1QG
UK

Authors' reply

Sir

We accept that the POSSUM physiological and operative scoring is described well enough in the literature to allow its application by independent investigators. However, to the best of our knowledge, this is not the case for the application of the predictor equations and the assessment of their goodness of fit to reported deaths.

In the absence of such guidance, we have utilized standard methods, well documented in the statistics literature, to assess the goodness of fit of both predictor equations[1–4]. It may be that Mr Copeland and co-workers use a different method of assessing the goodness of fit of their equation. However, in the absence of publication of their method, we are unable to comment on its relative validity. The Lemeshow–Hosmer methodology that we used produces an immediately meaningful comparison of predicted deaths with reported deaths, without having to resort to the complications and abstractions of receiver–operator characteristic curves and cut-off levels.

Messrs McIlroy and Copeland are incorrect in stating that 'simply calculating mean risk is not a valid method of predicting the total number of deaths'. Logistic regression is a form of discriminant analysis, which is intended to ascribe risks to individuals. It therefore follows that the sample population risk is the mean of the individual risks. Given that the risks can be applied to individuals, Mr Copeland's minimum risk of mortality of 1·08 per cent is too high a risk to ascribe to the fittest patients (physiological score 12) undergoing the most minor surgery (operative score 6). It may be that his method of analysis involves some extra stage or adjustment so that risks cannot be applied to individuals but only to the population above some arbitrary cut-off level, but this is not the case with our methodology.

POSSUM's usefulness as a research and audit tool lies in its ability to cope with differences in population and case mix between different surgeons and centres. If this is true it should not matter whether or not our sample population is fitter or is receiving relatively more minor surgery. We believe, however, that we presented reasonable evidence that our sample was representative of our general surgical workload at the time. We stated that day cases and paediatrics were excluded from our study. Emergency admissions were not excluded. Given that we used standard methods of analysis we would welcome publication of the method of analysis of Mr Copeland and co-workers.

D. R. Prytherch
M. S. Whiteley

Medical Physics Department
Portsmouth Hospitals NHS Trust
Portsmouth PO6 3LY
UK

1 Hosmer DW, Lemeshow S. Assessing the fit of the model. In: *Applied Logistic Regression*. Chichester: Wiley, 1989.
2 Hosmer DW, Lemeshow S, Klar J. Goodness-of-fit testing for multiple logistic regression analysis when the estimated probabilities are small. *Biometrical Journal* 1988; 30: 911–24.
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British Journal of Surgery 1996, 83, 1485

Book reviews

Year Book of Surgery 1995

Roshan Lall Gupta. 227 × 148 mm. Pp. 224. Not illustrated. 1996. New Delhi: Jaypee Brothers Medical Publishers. Price unavailable.

The *Year Book of Surgery 1995* is a collection of surgical abstracts gleaned from 20 journals, ranging from *The British Journal of Surgery* to *Tropical Gastroenterology*. The aim is to help teachers, practising surgeons and postgraduate students 'reorient their clinical approach in the light of new trends'. The book has been published in 1996 but, inevitably, the abstracts that are quoted were published in 1994. In approximately 10 per cent of the abstracts the editor has added an interpretive personal footnote. The rest of the abstracts are simply reproduced from the original journals. At first sight it is easy to be somewhat disparaging of a book of this type. In the Western world we have become so familiar with access to computer-based literature searches that no surgical trainee would use a book of this type. In order to get a more balanced response to the book, I sought the opinion of one of our surgical registrars from Pakistan It is important to realize that this volume sells in the Indian subcontinent for 200 rupees which is the equivalent of UK £5.00. It is possible that it may be of use to some surgeons in training who are approaching the second part of a surgical fellowship examination and who do not have access to recent journals or the time to glean the important articles. Such a trainee might find this small textbook to be stimulating and of some interest. It is not, however, truly comprehensive in that there is very little in the way of paediatric, vascular or orthopaedic surgery. This text will not be purchased by trainees in the Western world but it may have a limited market in the Indian subcontinent.

A. J. McKay
S. Mahmoud

Gartnavel General Hospital
1053 Great Western Road
Glasgow G12 0YN
UK

Prostatic Outflow Obstruction: Clinical Investigation and Treatment

P. J. Shah (ed.). 250 × 175 mm. Pp. 174. Illustrated. 1995. Oxford: Blackwell Science. £49.50.

Transurethral resection of the prostate (TURP) has largely superseded open surgery for benign prostatic obstruction, but it still carries small and significant mortality and morbidity rates. Hence the search continues for less invasive treatments with fewer side-effects, which may be suitable for treating this common condition at an earlier stage in the disease process. This book discusses modern diagnostic techniques for assessing prostatic obstruction, and evaluates the many new therapies tried in recent years in pursuit of these goals. These range from medical management (e.g. α-adrenergic blockers), through minimally invasive therapies (such as microwave hyperthermia), to alternative surgical procedures using laser ablation of the prostate, balloon dilatation or prostatic stenting. Modifications to existing surgical techniques to render TURP safer are also discussed. The authors draw largely on personal experience of evaluating these techniques at the Institute of Urology in London, complemented by review of the literature. As this subject is rapidly changing, some of the techniques described have already failed to meet initial expectations, while others, including laser therapy, have been developed considerably further. Nevertheless, this volume succeeds in providing a comprehensive review of an important topic that will interest both the urological trainee and the practising urologist.

G. N. A. Sibley

Bristol Royal Infirmary
Bristol BS2 8HW
UK

The Cambridge Dictionary of Statistics in the Medical Sciences

B. S. Everitt. 233 × 156 mm. Pp. 277. Illustrated. 1995 Cambridge: Cambridge University Press. £12.95.

This slim volume provides brief definitions of some 2000 statistical terms. I was consistently impressed by the precision of the definitions and had to look extremely hard to find examples to which I took exception. Even to browse through the dictionary is quite rewarding – I look forward to seeing articles in *The British Journal of Surgery* littered with 'sunflower plots' – and it does contain a thread of dry humour: 'Degrees of freedom (df): An elusive concept that occurs throughout statistics. Essentially, . . .'. The selection of entries for a dictionary is highly subjective and the author's selections appear to reflect more of an interest in statistical analysis than in the design or conduct of clinical trials. For example, there are several entries on minor aspects of analysis of variance (e.g. Mauchly's test), but no mention of numbers needed to treat, good clinical (research) practice, or standard operating procedures. If this dictionary has a weakness, it is that the definitions themselves often assume a fair degree of understanding of statistical concepts, I can see some clinicians locked into ever-decreasing circles as they follow up cross-references trying to understand the definition of the definition of the term where they started. I do not think that I could regard this as a 'must have' for all active clinical researchers However, anyone involved in refereeing or editing medical manuscripts will find it invaluable, saving hours by throwing immediate light on to unfamiliar statistical terms.

G. D. Murray

Robertson Centre for Biostatistics
Boyd Orr Building
University of Glasgow
Glasgow G12 8QQ
UK

Urology. 2nd ed.

J Blandy and C. Fowler. 282 × 220 mm Pp. 639. Illustrated. 1995. Oxford: Blackwell Science. £99.50.

It is a remarkable achievement for two authors to write a well referenced textbook of 633 pages covering the whole of urology, which is both up to date and easily readable; Blandy and Fowler have succeeded admirably. The volume is a second edition which is aimed at the young urologist starting out on his or her specialist training. It assumes nothing and starts at the beginning, with the first chapter on the armamentarium available to the urological surgeon today. Urological endoscopes, diathermy machines, lasers and lithotriptors are all described with helpful diagrams. Subsequent chapters look at the kidney, bladder, prostate, urethra and penis, testicle and adrenal. Each chapter is split into anatomy and physiology, followed by the disease processes that occur in the relevant organ There are a few criticisms. Although very well illustrated (in black and white) some of the radiographs are of poor quality and, occasionally, authoritative statements are made which are unsubstantiated. However, neither of these criticisms takes much away from a book that urological trainees will find immensely helpful.

D. Cranston

Churchill Hospital
Headington
Oxford OX3 7LJ
UK

Notices and announcements

8–20 October, 5–7 November, 3–5 December 1996
Fundamentals of Laparoscopic Surgery
Leeds, UK
Information S. Wilkinson, Leeds Institute for Minimally Invasive Therapy, Leeds General Infirmary, Leeds LS1 3EX, UK

13–19 October 1996
Recent Advances in Surgery of the Liver, Pancreas and Biliary System
Edinburgh, UK
Information: Marketing Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

19–24 October 1996
1st World Congress of Surgical Endoscopy
Beijing, China
Information J. M. Phillips, General Chairman, 1st World Congress of Surgical Endoscopy, 13021 East Florence Avenue, Santa Fe Springs, California 90670-8774, USA

21 October 1996
Continuing Medical Education. Breast Disease: Current Issues
Nottingham, UK
Information Nottingham National Breast Screening Training Centre, City Hospital, Nottingham NG5 1PB, UK

21–22 October 1996
'State of the Art' Surgery for Breast Specialists
Manchester, UK
Information Miss J. Smith, Department of Surgery, University of South Manchester, Nell Lane, West Didsbury, Manchester M20 8LR, UK

21–23 October 1996
4th Postgraduate Course in Surgery
Bangkok, Thailand
Information. V Sachakul, Secretary General, Local Organizing Committee, Department of Surgery, Pramongkutklao Hospital, 315 Rajvithi Road, Bangkok 10400, Thailand

23 and 24 October, 20 and 21 November 1996
Advanced Laparoscopic Surgery
Leeds, UK
Information· S. Wilkinson, Leeds Institute for Minimally Invasive Therapy, Leeds General Infirmary, Leeds LS1 3EX, UK

23–25 October 1996
Spinal Surgery Course
London, UK
Information· Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

24–26 October 1996
4th European Conference on General Thoracic Surgery
Cordoba, Spain
Information· Dr F. J. L. Pujol, C/.Caño, 3-1.°, 1, 14001 Cordoba, Spain

27–30 October 1996
8th Overseas Meeting of the Royal College of Surgeons of Edinburgh jointly with the College of Surgeons of Hong Kong
Hong Kong
Information. The Clerk to the College, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

3–8 November 1996
Urogynaecology: Principles and Practice Now
London, UK
Information Marketing Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

13–16 November 1996
3rd Hong Kong International Cancer Congress and the 7th Epstein–Barr Virus and Associated Diseases Congress
Hong Kong
Information· HKICC Secretariat, 2/F , Professorial Block, Queen Mary Hospital, Hong Kong

14–17 November 1996
3rd Congress of the International Association of Gerontology. European Region – Clinical Section
Thessaloniki, Greece
Information Athos City Congress, 5 Agias Sofias Street, Thessaloniki 54623, Greece

18 November 1996
Liver Symposium
London, UK
Information· Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

18–20 November 1996
Screening for Breast Cancer Multi-Disciplinary Course
Nottingham, UK
Information. Nottingham National Breast Screening Training Centre, City Hospital, Nottingham NG5 1PB, UK

18–22 November 1996
Annual Course in HPB Surgery
London, UK
Information. Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

19–22 November 1996
European Course on Laparoscopic Surgery
Brussels, Belgium
Information. Administrative Secretariat, Conference Services, Avenue de l'Observatoire, 3 bte 17, B-1180 Bruxelles, Belgium

20–22 November 1996
Vascular Surgical Society of Great Britain and Ireland 30th Annual Meeting
Bournemouth, UK
Information· Linda de Cossart, Countess of Chester Hospital, Liverpool Road, Chester CH2 1BQ, UK

23–24 November 1996
Transanal Endoscopic Microsurgery
Liverpool, UK
Information· J. O'Leary, Training Manager, MASTER Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

27–29 November 1996
British Association of Surgical Oncology Winter Scientific Meeting
London, UK
Information· Mrs V Hall, Administrator, BASO, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

4–7 December 1996
6th Alexis Carrel Conference on Chronic Rejection and Graft Atherosclerosis
Banff, Canada
Information Dr L. C. Paul, St Michael's Hospital, 30 Bond Street, Toronto, Canada M5B 1W8. UK

5–6 December 1996
Lung Volume Reduction for Emphysema. A Multidisciplined Approach
Treviso, Italy
Information: Dr G. Di Falco, 3 Divisione Chirurgica, Ospedale Generale Regionale, 31100 Treviso, Italy

6 December 1996
The Role of the Plain Abdominal Radiograph in the Acute Abdomen
Canterbury, UK
Information. Postgraduate Administrator, Kent Postgraduate Medical Center, Kent and Canterbury Hospital, Canterbury CT1 3NG, UK

2–6 March 1997
11th Biennial Congress – Asian Surgical Association Congress
Hong Kong
Information· Gloria Wong, Cancer Centre, Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

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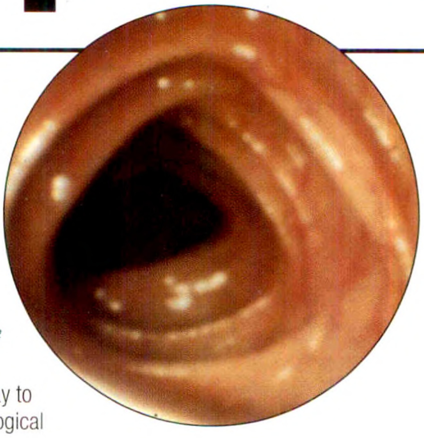

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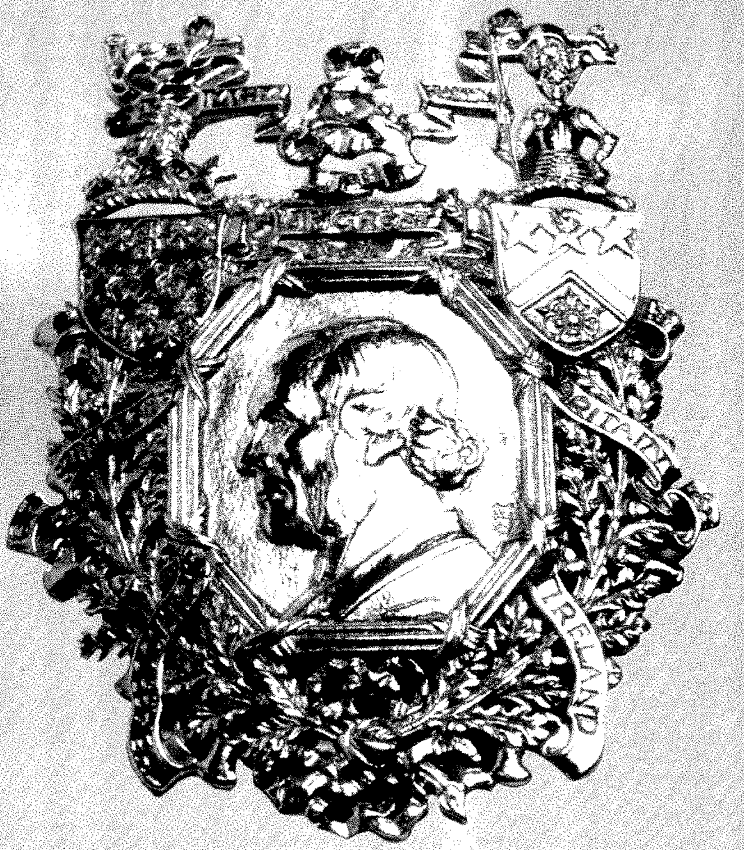

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Advertising enquiries should be directed to: Advertising Department, Blackwell Science Ltd, Osney Mead, Oxford OX2 0EL, UK. Telephone: 01865 206 206. Facsimile: 01865 200 918.

Subscriptions. The British Journal of Surgery is published monthly by Blackwell Science Ltd. Subscription prices for 1996 are: **Institutional** £114·50 (Europe), £128·50 (Overseas), $207 (North America); **Individual** £74·50 (Europe), £84 (Overseas), $135 (North America); **Trainee** £34·50 (Europe), £39 (Overseas), $63 (North America). Subscribers in Canada must add 7% to the subscription price to allow for GST. Subscribers in Europe must quote their VAT registration number or state that they are not registered. Subscribers in the following countries who are not VAT-registered must add VAT at the appropriate rate: Belgium (6% TVA/BTW); France (2·1% TVA); Germany (7% MWST); Spain (4% IVA); The Netherlands (6% BTW). Orders for current subscriptions and back issues should be sent to Blackwell Science Ltd, Journal Subscriptions, PO Box 88, Oxford OX2 0NE, UK. Telephone: 01865 206180 or 206038; Facsimile: 01865 206219; E-mail: journals.cs@blacksci.co.uk. Information on this journal and other Blackwell Science publications is available on the Blackwell Science Homepage: http://www.blackwell-science.com.

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s; superinfection; phlebitis, throm-
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njection. Less frequent: muscle
or weakness; hallucination; dry
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e of preparation: March 1996.

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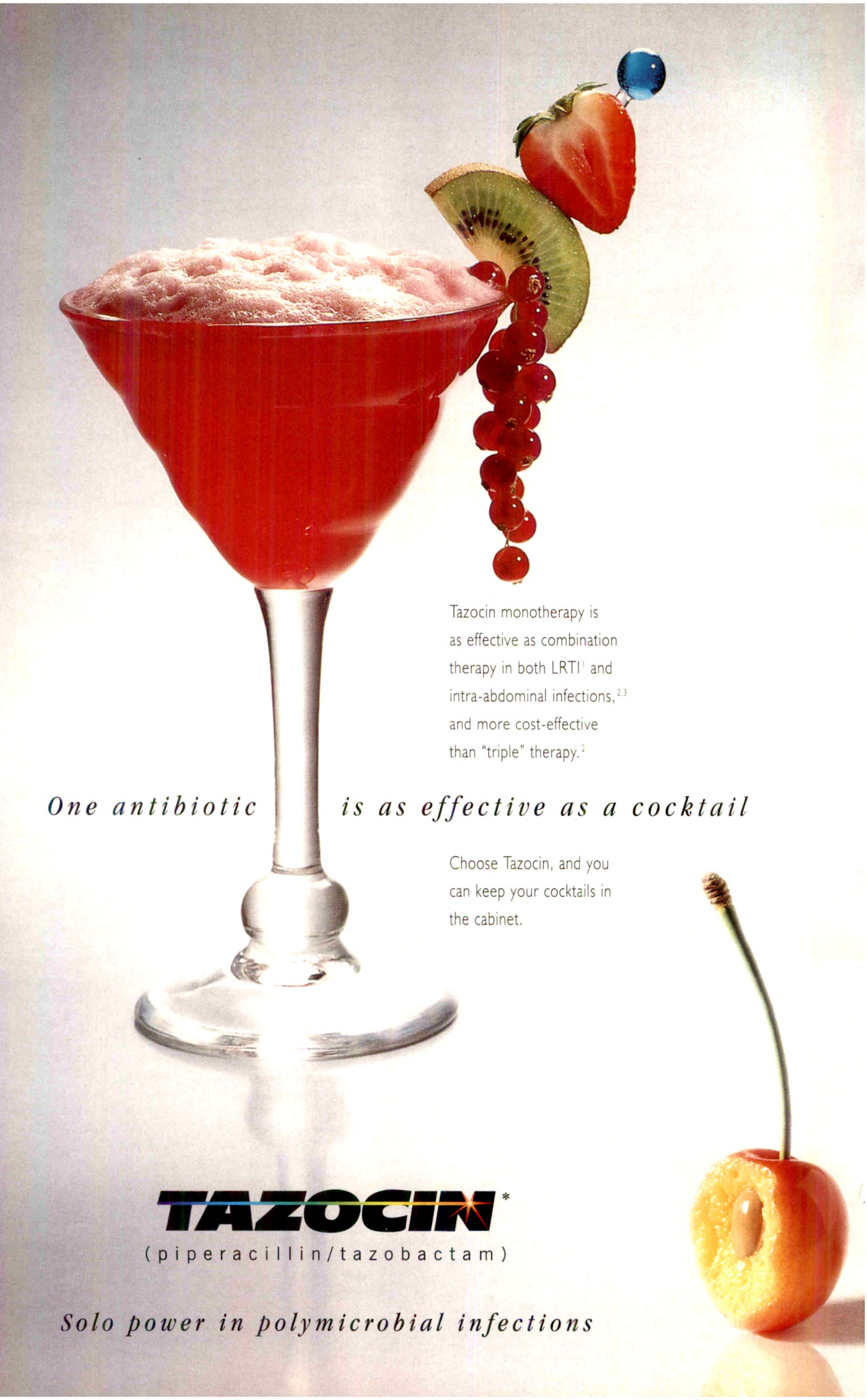

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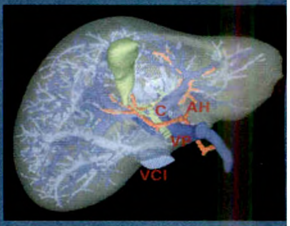

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Crawford William Jamieson MS, FRCS

The British Journal of Surgery has been remarkably fortunate with its last three chairmen, who have moulded the Journal from a parochial news-sheet into an important international publication of renown. Each has placed his mark on the Journal, and each has provided a degree of stability to its affairs, such that the Journal is now wholly owned by the British Journal of Surgery Society (and therefore by British surgery). When Crawford Jamieson joined the organisation as Assistant Editor in 1977 the BJS was owned by John Wright, the Bristol publisher, in partnership with the BJS Society. That partnership had been formed by the first editor Ernest Hey Groves and John Wright, reputedly in a coffee shop in Bristol; no written record of the agreement existed. By wise and skilful negotiation, Leslie LeQuesne formalised the arrangement with a buy-out clause, largely orchestrated by the then Treasurer, Hugh Dudley. Preparations for the buy-out were set in hand for early in 1983 by which time Hugh Dudley had taken over as Chairman. The managing director of John Wright, aware of possible change, invited the editors to a pre-Christmas lunch. Well briefed by the Chairman, the editors held true to the line; the Editor, Crawford Jamieson, displaying his qualities of tact, diplomacy, suave urbanity and sound business sense, kept the conversation firmly in the field of play. Perhaps, Crawford displays his talents best at the dinner table, guiding conversation and directing business to a successful conclusion. Once John Wright had been set aside, the Journal was published by Butterworth and Co. until the next contract was ripe for negotiation. With skill, firmness and foresight, that contract was established with Blackwell Science Ltd by Crawford Jamieson in his capacity as Chairman. The Journal has benefited enormously from this agreement with BSL, as has British surgery through the British Journal of Surgery Society Ltd.

Crawford has guided the BJS as Chairman since 1988, having previously been Assistant Editor to Mr Felix Eastcott in 1977, and Editor from 1978 to 1987, years of growth and influence within the Journal. His experience as Editor enabled him to maintain an intimate knowledge of BJS affairs, yet leave the Editor to run the Journal. The arrangement within the BJS is that it is managed by the British Journal of Surgery Society, which deals with all the business affairs, including any profit that accrues from its publication. The Chairman chairs the meetings of the Council of the Society at which all business matters are discussed and any profits are distributed within British surgery. The Editorial Committee is also chaired by the Chairman, but at the meeting of this committee publishing, promotion and policy of the Journal are considered with the publishers. For instance, the discussion on the size of the Journal and the standing in the citation index are hotly debated, rigid views being tempered with an anecdote from the Chairman related to fish or fowl or surgery.

The skill of the Chairman lies in balance and decisiveness, talents that Crawford has shown throughout his long service. Like his predecessors he has given unstinting diligence, devotion and humour to the affairs of the BJS.

R. C. G. Russell
Chairman
British Journal of Surgery Society

Mr Christopher Russell, a former Editor of the Journal, has taken over from Mr Jamieson as Chairman of the Editorial Board since May 1996.

R. C. N. Williamson
Senior Editor

British Journal of Surgery 1996, 83, 1490–1491

Leading articles

Technique of hepatectomy

In the past two decades hepatectomy has evolved from a rough, hasty and bloody procedure that could be performed only by a few experts to a refined, deliberate and relatively bloodless operation that can be carried out by many trained general surgeons. The operative mortality rate for cirrhotic patients has decreased from 58 per cent in Foster's survey in 1977 to less than 5 per cent in many recent series. The 5-year survival rate after hepatectomy for hepatocellular carcinoma (the most common indication for hepatectomy in the East) has also improved to about 50 per cent[1]. Although it may be argued that some improvement in survival is related to the lead-time bias associated with resecting small tumours in patients with good liver function, the major contributory factor to early success is improved surgical technique. Numerous technical innovations relating to hepatectomy have now been reported. They aim to increase the resectability rate by including nearby organs, major blood vessels or bile duct affected by the malignancy[2] and to allow surgery on high-risk patients, for example those with bile duct obstruction, intrahepatic recurrence or suboptimal hepatic function[3]. Such heroic approaches will benefit only a fortunate few, because the prognosis of patients with advanced malignancy and cirrhosis is usually dismal. Unless a substantial period of good quality of life is attained, the classical criteria for selection of patients for hepatectomy must hold, i.e. unilateral disease and sufficient liver function.

At present the technique of hepatectomy is fairly standardized but variation in special circumstances should be exercised to achieve the best results. Surgeons should aim at reducing blood loss, ensuring an adequate tumour-free resection margin and protecting the liver from hypoxic injury. Massive bleeding has been recognized as detrimental, but this can generally be avoided nowadays. However, avoidance of exogenous blood transfusion should be the ultimate aim because such transfusion adversely affects long-term survival[4]. An adequate tumour-free resection margin can be marked out accurately using intraoperative ultrasonography on the surface of the liver, but adequate resection can be achieved only if the ultrasonic dissector is applied carefully during liver transection. Unexpected liver function impairment may be due to inadvertent and prolonged application of a retractor over the hepatoduodenal ligament or rotation of the liver lobe[5], both of which should, therefore, be avoided.

Excellent exposure of the liver can generally be achieved using a bilateral subcostal incision and a self-retaining retractor. The right lobe can be mobilized and rotated to the wound surface if necessary. This manoeuvre is easy when there is a soft and normal liver, but it is potentially dangerous in the presence of a large cancer as the space for manipulation is limited. During exposure for segmentectomy of segment 7 or 8, prolonged rotation of the liver is undesirable because the inflow and outflow pedicles will be twisted[5]. In such difficult situations a thoracic extension to the subcostal wound or a J incision[6] should be favoured to allow the liver transection plane to be perpendicular to the wound.

Preliminary hilar dissection is necessary for division of the ipsilateral inflow vasculature for lobectomy. In the case of segmentectomy, it may be used for hemivascular control or the intrahepatic posterior approach[7]. Dissection of the right or left hepatic duct within the hilar plate is not desirable as it may damage the blood supply to the bile duct. Division of the hepatic duct is best left to the stage of parenchymal transection at the liver hilum, by which time the hepatic duct can be seen clearly and ligated with the tissue of the hilar plate.

Control of the right hepatic vein outwith the liver is difficult when dealing with a large tumour of the right lobe. Forceful mobilization of the liver will disseminate cancer cells or lacerate the right hepatic vein or inferior vena cava. Transection of the liver from its anterior surface down to the anterior surface of cava without prior mobilization (anterior approach) may be advantageous in this situation[8]. Such an approach can be accomplished only with an ultrasonic dissector, as it is difficult to transect liver tissue in front of the inferior vena cava using a crushing clamp or finger fracture technique. The ultrasonic dissector facilitates liver transection by allowing a clear exposure of the blood vessels, which permits a reduction in blood loss and a wider tumour-free resection margin[9]. However, its use is time consuming and may not be entirely bloodless, especially when a high power is set. Furthermore, it may be associated with spread of viral hepatitis. The ultrasonic dissector is, therefore, not the final answer for hepatectomy; better equipment design is still desirable.

The Pringle manoeuvre is regarded as an efficient method of reducing blood loss during liver transection, but up to now there has been no prospective randomized trial confirming its absolute safety and efficacy. It is worthy of note that hepatectomy is increasingly being performed without inflow occlusion[3]. Cirrhotic livers, in particular, are probably more vulnerable to ischaemic injury than normal livers and surgeons should acquire the skill of transecting the liver without a Pringle manoeuvre to avoid ischaemic damage in such a situation. It is questionable whether the Pringle manoeuvre is needed after control of the inflow pedicle to the tumour-bearing lobe, because most bleeding then comes from the hepatic vein. Attempts have been made to produce a completely dry field by total (inflow and outflow) vascular occlusion, with or without supracoeliac aortic clamping, but the amount of bleeding during and after liver transection was not encouraging[10]. The ability to transect the liver safely without inflow and outflow vascular occlusion is a prerequisite for harvesting a left lobe graft in living-related hepatic transplantation. Mastering the technique of the anterior approach using the ultrasonic dissector opens the possibility of harvesting a right lobe graft from a living relative for transplantation into an adult recipient.

Despite several major advances in the technique of hepatectomy in the past decade, only vigilant attention to technical detail, together with careful perioperative management, leads to success. There is virtually no room for error in this challenging field of surgical activity.

S. T. Fan

Department of Surgery
The University of Hong Kong
Queen Mary Hospital
102 Pokfulam Road
Hong Kong

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British Journal of Surgery 1996, 83, 1492–1493

The venous perforator

Phlebology is plagued, more than most specialties, with eponymous nomenclature. So it is, for example, that we have the lower-limb operations of Linton, Rob and Cockett to deal with superficial to deep venous connections, named according to their locations for Dodd, Bassi, Boyd or Hunter.

It has long been observed that the skin changes of chronic venous insufficiency (lipodermatosclerosis) are associated with conspicuously enlarged and incompetent perforating veins, notably at the medial border of soleus in the lower calf. This group of perforators is sometimes referred to as Dodd's perforators. The surgical instinct has been to attack them, on the assumption that they are causally related to the skin changes. Surgical onslaughts have taken a variety of forms, the more radical of which are subfascial ligation, as described by Linton[1] and Rob[2], and extrafascial ligation popularized by Cockett[3]. These operations, through incisions which often extend most of the length of the calf, require prolonged postoperative rest and limb elevation; they incur substantial early healing problems and late scar breakdown. Although a few authors have claimed satisfactory long-term results, such procedures have tended to fall from favour in recent years. Perforator interruption, by whatever method, has never to our knowledge been evaluated by clinical trial.

Endoscopic subfascial surgery is a neat alternative that has attracted attention recently in several countries, although it has been well known in Germany for around a decade. It was developed by Hauer[4], popularized by Fischer[5], and utilized in large series by Jugenheimer[6] and Sachs *et al.*[7]. The technique is relatively simple and is performed along with saphenofemoral ligation, thigh stripping and multiple phlebectomy. Through a small incision in the upper calf, well clear of any lipodermatosclerosis or ulceration, an endoscope is introduced between the deep fascia and the underlying muscle. The instrument is then advanced down to intercept incompetent perforating veins, which may be clipped, treated with diathermy or simply cut. In this way a previously formidable operation has been transformed into a minimally invasive procedure that can even be performed on a day-case basis. The problem is that this is an operation without clear indications. The fact that varicose veins exist, with or without skin complications, and are connected to the deep veins by perforators does not necessarily mean that such perforators are incompetent or that they need to be intercepted. Indeed emerging evidence suggests that perforator surgery may have an extremely limited place.

Perforators in health convey blood predominantly in an inwards direction, filling the intramuscular veins during muscle-pump diastole. When the perforator valves become incompetent in chronic venous insufficiency, as Bjordal's elegant studies showed[8], there is a bidirectional flux through incompetent perforating veins with a predominantly outward flow, which renders the calf pump inefficient. However, by simultaneously measuring pressure in deep, superficial and perforator veins of patients with varicosities and incompetent perforators, Bjordal also showed that perforator incompetence contributed little to ambulatory venous hypertension: when retrograde flow in the main saphenous vein trunk was interrupted by proximal saphenous occlusion, venous pressure at the ankle became normal. These observations are supported by the clinical studies of Stacey *et al.*[9], which demonstrated that laboratory measurements of venous function do not return to normal as a result of perforator surgery. Åkesson *et al.*[10], by performing superficial saphenous surgery and perforator surgery as two separate procedures, showed an improvement in superficial reflux and venous hypertension after superficial vein surgery, but no additional improvement was noted when perforator surgery was added. A further spanner has recently been thrown into the works by Campbell and co-workers[11] who, by means of duplex ultrasound studies before and after conventional varicose vein surgery to the superficial system, without perforator surgery, have shown that 80 per cent of incompetent perforating veins regain competence after operation.

It is interesting too to note that Zukowski *et al.*[12] have described 35 per cent of their patients with chronic venous disease as having, on duplex ultrasonography, the combination of incompetent perforators plus incompetent valves in the deep veins from the popliteal vein downwards. The importance of incompetence of the popliteal vein 'gatekeeper segment' has been highlighted in other recent studies relating popliteal incompetence to impaired ulcer healing and poor prognosis after subfascial ligation[13].

So it seems clear that indiscriminate interception of incompetent perforators cannot be justified. The availability of duplex scanning and endoscopic subfascial techniques offers opportunities to put this component of venous surgery on a rational footing. Several further types of studies are required. First, there is a need to confirm the relationship between superficial and (especially) deep vein incompetence and haemodynamically significant incompetent perforating veins. Second, comparisons of diagnostic techniques for identifying perforators could be combined with validation of the accuracy with which endoscopic surgery can locate and interrupt them. Finally, clinical trials are needed to compare the outcome of perforator interception and perforator sparing, in defined patient groups. Evidence-based medicine has not so far been a strong feature of phlebological practice.

C. V. Ruckley
K. R. Makhdoomi

Department of Surgery
Royal Infirmary
Edinburgh EH3 9YW
UK

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British Journal of Surgery 1996, 83, 1494–1504

Review

Desmoids in familial adenomatous polyposis

S. K. CLARK and R. K. S. PHILLIPS

The Polyposis Registry, St Mark's Hospital, Northwick Park, Watford Road, Harrow, Middlesex HA1 3UJ, UK
Correspondence to: Mr R. K. S. Phillips

Clinical desmoid disease affects approximately 10 per cent of patients with familial adenomatous polyposis (FAP); the subclinical rate is unknown. Desmoids are probably neoplastic rather than regenerative in origin and may arise in association with germline or somatic mutations at or beyond codon 1444 of the *APC* gene. Intra-abdominal desmoids behave unpredictably but are an important cause of death in those with FAP. Signal intensity on magnetic resonance imaging reflects tumour cellularity, which in part determines progression, and this may help management. Surgical treatment of advanced desmoids is hazardous, but medical treatments have limited success. Chemotherapy with doxorubicin and dacarbazine is currently under evaluation.

Desmoid tumours are a heterogeneous group of benign fibrous masses, at times clinically aggressive and even life threatening. They are classified as fibromatoses, a group of pathologies[1] resulting from proliferation of well differentiated fibroblasts that infiltrate and show repeated local recurrence but are neither unequivocally malignant nor inflammatory. Other fibromatoses include palmar, plantar and penile fibromatosis, keloids and low-grade fibrosarcoma.

The nomenclature and classification of desmoids is complex and confusing. Terms including aggressive fibromatosis, mesenteric fibromatosis and fibrosis are used to refer to these lesions. Classifications used by different authors vary subtly, making comparison difficult. Desmoids occur in association with familial adenomatous polyposis (FAP) or sporadically, and may be subdivided by site into extra-abdominal, abdominal wall or intra-abdominal[2]. There are differences in behaviour between FAP-associated and sporadic desmoids. Unfortunately, the literature often mixes desmoids and other fibromatoses, and includes FAP-associated with sporadic desmoids, making no distinction between these, and sometimes failing even to mention FAP.

Epidemiology

Desmoids are rare, accounting for less than 0·1 per cent of all tumours[3,4], with an annual incidence of 2–4 per million[5]. About 2 per cent of desmoids are FAP associated and patients with FAP are at about 1000-fold increased risk of developing desmoids compared with the general population[6]. Incidences from 3·6[7] to 13[8] per cent have been reported by various polyposis registries; 10 per cent of patients with FAP attending the Cleveland Clinic are actually being treated for desmoid tumours[9]. Both sporadic and FAP-associated desmoids have a peak incidence between 28 and 31 years of age, the reported range being from 5 months to 80 years. Sporadic desmoids are significantly more common in women, with a female:male ratio ranging from 2:1 to 5:1, but in FAP any sex difference is less marked[6,8,10–12], non-existent[13,14] or even reversed[15,16].

Paper accepted 12 June 1996

Desmoid disease is an important cause of morbidity and mortality in FAP, life-table analysis of patients with intra-abdominal desmoids at St Mark's Hospital revealing an overall 10-year survival rate of 63 (95 per cent confidence interval 44–82) per cent (*Fig. 1*). Desmoid-associated mortality rate in FAP ranges from 10 to 50 per cent[11,16,18,19], with a mean interval from diagnosis to death of 4[20] to 6[21] years. In one large study[21], desmoid disease was the second commonest cause of death overall in patients with FAP (10·9 per cent), after colorectal carcinoma (58·2 per cent). In patients who had prophylactic colectomy, desmoid disease was the commonest cause of death (30·6 per cent), periampullary carcinoma being second (22·2 per cent), with desmoid-related death occurring significantly sooner after colectomy and at a significantly younger age than death from other causes. Other studies have confirmed desmoid disease as either the commonest[22,23] or second commonest[24,25] cause of death overall after colorectal cancer in patients with FAP, and either the commonest or second commonest[24,26] single cause of death after prophylactic colectomy. Desmoids can also contribute to death from other causes by making surgery for rectal or

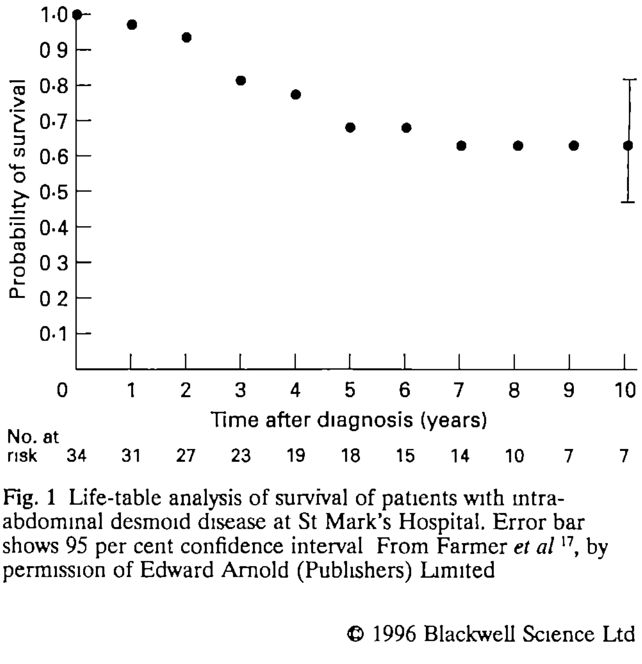

Fig. 1 Life-table analysis of survival of patients with intra-abdominal desmoid disease at St Mark's Hospital. Error bar shows 95 per cent confidence interval. From Farmer *et al* [17], by permission of Edward Arnold (Publishers) Limited

upper gastrointestinal malignancy difficult or even impossible[15,27].

Aetiology and genetics

Three factors, initiation by trauma, the influence of sex steroids and an underlying inherited defect, have been implicated in the aetiology of desmoids, although their precise role is unclear.

Trauma

Of intra-abdominal and abdominal wall desmoids in FAP, 68–86 per cent occur after abdominal surgery, the majority (55–75 per cent) within the first 5 years[6,8,11,15,16,28,29]. The average interval between surgery and the diagnosis of desmoid is 2–3 years, the reported range being 4 months to 28 years. The suggestion that the more extensive dissection in restorative proctocolectomy compared with ileorectal anastomosis might result in a higher incidence of subsequent desmoids is not borne out in the literature[15]. Despite the strong association with previous surgery, intra-abdominal desmoids can occur spontaneously in FAP[28], being found in 4 per cent of patients at the first laparotomy[15]. Only 30 per cent of sporadic abdominal wall desmoids occur after trauma[29] and these frequently arise in surgical scars[30]

Sex steroids

Oestrogens seem to stimulate the growth of sporadic desmoids in particular and abnormal oestrogen metabolism is also implicated in the pathogenesis of palmar fibromatosis, a related condition[31]. There is a higher incidence of desmoids in females, particularly those of reproductive age, and an apparent tendency for them to develop, especially in the abdominal wall, during or soon after pregnancy[3,4,32–34] or while taking combined oral contraceptives[14,31,35,36]. Any relationship between intra-abdominal desmoid and pregnancy has been questioned however[12,37]. The fastest growth rate is observed in young women[29], who also have the highest rate of recurrence of extra-abdominal desmoid after excision[38]. There have been reports of regression after the menopause[5,36,39] and after oophorectomy[40]. A case report has described an abdominal wall desmoid developing in a man treated with oestrogen for carcinoma of the prostate[41] which regressed after treatment was stopped. Desmoid-like lesions also occur in laboratory animals given oestrogens[42–44] and these can be suppressed with progestogens[42].

Oestrogen binding sites have been identified in 25–75 per cent[29,45,46] of mixed desmoids. Some desmoid cell cultures grow and produce collagen in response to oestrogen and are inhibited by the antioestrogen tamoxifen[47]. Recently, extra-abdominal desmoids have been found to express platelet-derived growth factor β, a potent mitogen for mesenchymal cells not normally produced by fibroblasts. This expression was increased by oestrogens[48].

Genetics

Sporadic desmoids do not seem to have a familial tendency, but Reitamo[49] found another abnormality of connective tissue (e.g. dental abnormalities, exostoses, incomplete spinal segmentation) on radiography in 80 per cent of patients with sporadic desmoid, compared with 7 per cent of normal controls, suggesting a basic functional inherited defect in connective tissue formation. Some familial clustering of desmoids in patients with FAP has been noted[8,10,20,32,50–53] and an increased risk of developing desmoids in first-degree relatives has been identified[6].

FAP, an autosomal dominant condition, can be considered to be a generalized disorder of tissue growth regulation caused by germline mutation in one copy of the *APC* gene. The *APC* gene has been localized to chromosome 5q22[54,55], cloned and sequenced[56–58], and mutations have been identified. It is estimated that about 10 per cent of cases of FAP arise as a result of a new mutation[59]. *APC* is a large gene consisting of 15 exons; exons 1–14 are small and exon 15 contributes 77 per cent of the coding region (codons 653–2843). The APC protein product localizes to the cytoplasm in epithelial cells[60] Although its precise function is not known, this protein associates with α and β catenins, which bind to cell-surface E cadherin and contribute to its role in cell adhesion and interaction[61,62]. APC protein is also thought to be important in formation of microtubules[63,64], which anchor the cytoskeleton and play a part in cell division. Most *APC* mutations occur between codons 900 and 1600, and almost always give rise to premature stop codons, resulting in a truncated protein product.

There is evidence of genotype–phenotype correlation in FAP: mutation at codon 1309 and large numbers of colonic polyps[65]; mutation at codons 1250–1464 and earlier death from colorectal cancer[66]; mutation 5′ of codon 160 and attenuated colonic polyposis[67]; mutation 3′ to a boundary in exon 9 and congenital hypertrophy of the retinal pigment epithelium[68]. Desmoids have been reported to occur more frequently in patients with mutation 3′ to codon 1444[69,70].

Wild-type APC protein is believed to form active oligomers, interaction between normal and mutant APC perhaps blocking function[71] to an extent related to the structure of the truncated protein. Proximal (5′) mutations result in severely truncated protein that may fail to oligomerize with the wild-type product of the remaining normal gene and thus have little effect on its function. More distal (3′) mutations result in a less truncated protein, which could interact significantly thereby impairing function. This ‘dominant negative’ effect may be further complicated by varying stability of the truncated APC protein in different tissues and subnormal levels of wild-type protein produced by the single remaining normal *APC* gene[66,72].

Identical mutations may be associated with diverse phenotypes[56,73], so genetic modifiers are probably involved in determining phenotype, as in the Min mouse[74]. Environment also influences phenotype, evidenced by polyp regression after colectomy[75].

Fibroblasts cultured from skin biopsies from patients with FAP[76–78] show similar defects in organization of cytoplasmic actin to those of tumour fibroblasts[79], abnormalities of growth pattern, and increased susceptibility to viral transformation, supporting the view that desmoid tumours are a phenotypic variant of FAP due to an abnormal fibroblastic response caused by the effects of the germline mutation.

An important step in the adenoma–carcinoma sequence is a somatic mutation (‘second hit’) in the remaining normal *APC* gene in the colonic epithelium[80,81]. A clonal deletion of 5q bearing the normal copy of *APC* has been identified in an intra-abdominal desmoid in FAP[82]. Loss of heterozygosity in 5q21–22, indicating loss of wild-type *APC*, has also been demonstrated[83,84]. Bridge *et al.*[85] described frequent clonal chromosomal rearrangements, especially 5q deletion, in fibroblasts from sporadic and FAP-associated desmoids. Almost all reported somatic mutations in desmoid tumours are deletions in exon 15[86,87] and lead to a downstream premature stop codon. Other abnormalities identified in sporadic desmoids include loss of chromosome 4[85] and trisomy 8[88,89], both of which have also been described in palmar and penile fibromatosis, and multiple complex chromosomal abnormalities[90]. There is thus some evidence that desmoids may result from a 'second hit' mutation followed by clonal expansion and therefore are true neoplasms.

A recent study[86] suggested that one of the two *APC* mutations in desmoids occurs at or beyond codon 1444, producing APC protein product of at least a certain length. This is irrespective of whether the mutation was inherited in the germline and is, therefore, present in all cells of the body, or was the result of a somatic mutation and clonal expansion.

Pathology

Desmoid tumour pathogenesis is not clearly understood. Desmoids may occur in any musculoaponeurotic structure, but the distribution varies markedly between those occurring in FAP, of which about 70 per cent are intra-abdominal, 15 per cent in the abdominal wall and 15 per cent extra-abdominal[6,11,14,28], and others where the abdominal wall (about 50 per cent) and extra-abdominal sites (40 per cent) predominate and only a minority are intra-abdominal (10 per cent)[91,92]. About 80 per cent of intra-abdominal desmoids are in the small bowel mesentery. Other sites documented include the transverse mesocolon, ligamentum teres and retroperitoneum[93]. In 5–38 per cent of cases multiple sites are involved[6,14,92,94]. Intra-abdominal desmoids most often give rise to life-threatening complications and are most difficult to treat, which explains why desmoids pose such a problem in FAP.

Mesenteric desmoids probably arise as flat white plaques and strands which contract, tethering the bowel and causing thickening and puckering of the mesentery. Further progression results in a discrete lobulated mass[8,95] (*Fig. 2*). There is no true capsule and the desmoid grows, compressing and infiltrating surrounding tissues such that the infiltrative margin may extend several centimetres beyond the palpable tumour edge. Eventually small bowel, ureters and mesenteric blood vessels may become encased and obstructed. Desmoids range in size from a nodule a few millimetres in diameter to a large mass. The cut surface is usually pinkish-white, often whorled, and may show evidence of cystic degeneration or haemorrhage, especially in large tumours.

Desmoids usually grow slowly but the rate varies during the course of the disease and they may behave somewhat more aggressively when associated with FAP[96]. Church[95] has suggested that 10 per cent of intra-abdominal desmoids in FAP disappear spontaneously, 29 per cent undergo cycles of growth and resolution, 47 per cent remain stable after diagnosis and 10 per cent grow rapidly. They do not metastasize and the only reliable report of malignant change occurred after radiotherapy[97]. Spontaneous regression has been documented in 4–17 per cent[11,49,98].

Histologically, desmoids consist of mature, highly differentiated fibroblasts in an abundant collagen matrix[99] (*Fig. 3*). Aggregates of lymphocytes are frequently located at the margins. There is a wide range of cellularity, often with acellular areas towards the centre of the tumour and a densely cellular periphery which can be mistaken for fibrosarcoma. Many of these cells are myofibroblasts[100,101], which are also found in repair tissue and malignant tumour stroma[102]. The cells have ill defined cytoplasm and pale nuclei. Mitoses are rare and nuclear atypia is absent. Electron microscopy has shown extensive intracellular collagen fibrillogenesis in the Golgi complexes of desmoid cells. This process usually occurs outside cells where collagen is formed from precursors secreted by the cells[103,104].

Presentation and complications

Desmoids are often asymptomatic and an incidental finding on examination or at laparotomy. They can be

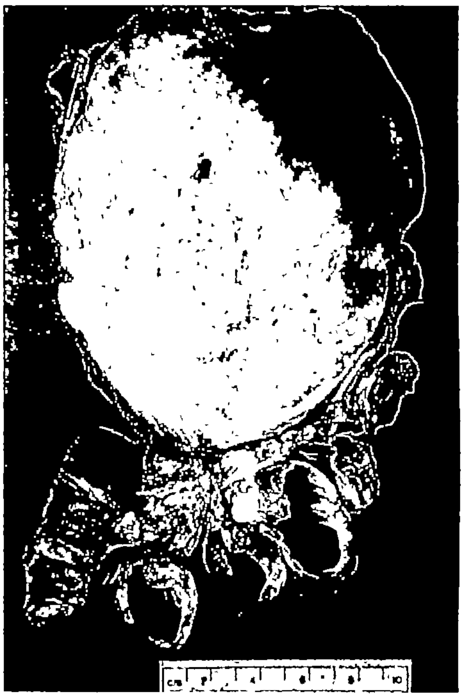

Fig. 2 Operative specimen of a desmoid arising within the small bowel mesentery

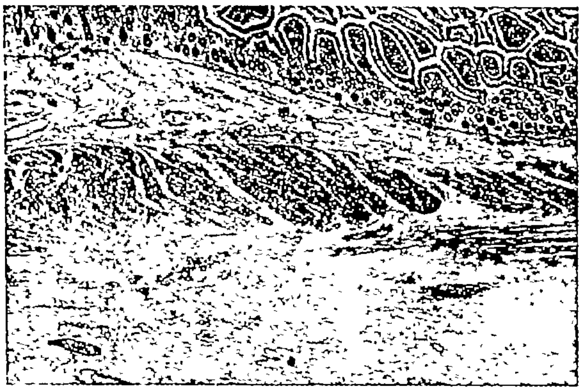

Fig. 3 Desmoid infiltrating the muscle of the small bowel (Masson trichrome, original magnification ×100)

very large before causing symptoms and may present simply as a mass. About one-third of intra-abdominal desmoids cause pain. Tethering and compression of the small bowel can cause obstruction, so progressive cachexia is a frequent problem. The mesenteric blood vessels may become occluded causing small bowel ischaemia[31], and central necrosis sometimes occurs within the desmoid. Fistula and sepsis may supervene[105,106] and are important causes of mortality.

Compression of large veins results in deep venous thrombosis; nerve compression can cause pain and sensory and motor deficits. Ureteric obstruction is common and respiratory failure[31], upper gastrointestinal bleeding[107] and aortic rupture[21] have been reported. Penna *et al.*[15] reported that 27 per cent of intra-abdominal desmoids cause hydronephrosis, perforation, impaired pouch function or obstruction requiring laparotomy. Desmoids found at laparotomy may interfere with planned surgery, preventing restorative surgery[108] or even resection of malignancy[109]. Some patients with FAP present with a desmoid before the colonic polyposis is detected[8,14,110], making investigation of the large bowel essential when an apparently sporadic desmoid is diagnosed.

Investigation

Laparoscopy caused bowel perforation in one study of chemotherapy for intra-abdominal desmoids[111] and cannot be recommended. Biopsy anecdotally has been implicated in accelerating tumour growth, but desmoid progression is notoriously variable and series in which several were biopsied do not support this[8]. Fine-needle aspiration cytology may be used, but histological confirmation is recommended, particularly to differentiate desmoid from low-grade fibrosarcoma[112,113].

Desmoids do not calcify, appearing on plain radiographs as a soft tissue mass displacing bowel loops. Intravenous urography and barium studies have been superseded by contrast-enhanced computed tomography (CT), which images the desmoid itself, although the former have some limited use in follow-up after surgery for bowel or ureteric obstruction. Angiography outlines neighbouring major blood vessels while also showing the usually sparse tumour vasculature, which contrasts with the extensive neovascularization of poorly differentiated sarcomas[114], but this investigation has also been largely replaced by enhanced CT.

Ultrasonographic scanning to investigate abdominal wall[115] and intra-abdominal desmoids[116,117] can localize a mass, but CT is required to demonstrate soft tissue density. Mesenteric desmoids appear as well demarcated solid masses with varying degrees of echogenicity due to mesenteric fat, blood vessels and cystic degeneration, but changes are not specific and cannot be used to distinguish a desmoid from mesenteric lymphadenopathy, lipoma or sarcoma.

Several radionuclides are taken up by desmoids. [^{99m}Tc(V)]dimercaptosuccinic acid is taken up more reliably than gallium-67 citrate and has the advantage that scanning can be done hours rather than days after injection[118]. This type of imaging may be useful in follow-up after treatment as it has greater sensitivity than CT in the differentiation of residual scarring from active disease[119,120].

CT is now the best choice for investigating intra-abdominal desmoids; the appearances have been well described[94,116,121–123]. Early mesenteric lesions appear as ill defined soft tissue infiltration of mesenteric fat (*Fig. 4*). Later, a mass (as small as 2–3 cm) may be seen, with displacement, infiltration (with the appearance of 'whiskers' extending into the mesenteric fat), tethering and encasement of small bowel loops. Desmoids show mixed attenuation and variable enhancement. Computed tomographic appearances correlate poorly with symptoms in intra-abdominal desmoids, but tumour diameter greater than 10 cm, multiple mesenteric tumours, bilateral hydronephrosis and extensive small bowel involvement are poor prognostic markers[123]. Abdominal CT may show regression of bulky tumours, but small bowel matting and adhesions following colectomy may be difficult to distinguish from residual or recurrent desmoid[111].

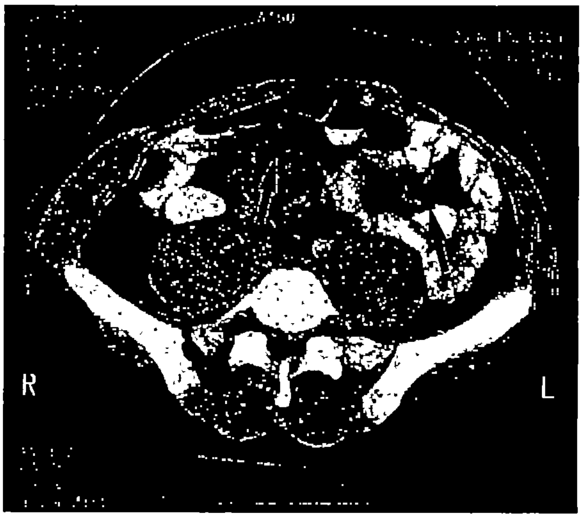

Fig. 4 Computed tomogram showing early desmoid in the small bowel mesentery

Magnetic resonance imaging (MRI) has advantages when investigating extra-abdominal desmoids[124–127]. Not only does it have multiplanar imaging capabilities, but contrast resolution is superior to that of CT, particularly in the presence of postoperative or radiotherapy changes[127]. The MRI features of both extra-abdominal[128,129] and abdominal wall[130] desmoids have been documented. The image intensities are heterogeneous, but overall there is low or similar signal intensity relative to muscle on T_1-weighted images and variable signal intensity on T_2-weighted images. There is good delineation of vascular involvement and variable enhancement with gadolinium–diethylenetriamine penta-acetate[131]. T_2-weighted sequences correlate best with histological findings[129,132,133]; high signal intensity is associated with increased cellularity, and low intensity is due to parallel orientation of abundant collagen and decreased density of mobile proteins in relatively acellular areas. Perhaps active cellular areas within desmoids might be detected by means of T_2-weighted sequences, thereby aiding prediction of tumour growth.

Treatment

Treatment is controversial, empirical and difficult. It is based largely on anecdotal reports and small, poorly controlled studies of predominantly sporadic desmoids, most of which are retrospective, encompassing long time spans, changing techniques and varying in follow-up. Many lack detailed information on desmoid site or FAP status.

Surgery

Surgery is widely accepted as the first-line treatment for extra-abdominal and abdominal wall desmoids, despite recurrence being common (20–80 per cent)[2,11,18,34,49,134]. The infiltrative nature of the lesion makes completeness of excision difficult to judge clinically, but there is controversy over the importance of excision margins. Some series[19] show a higher recurrence rate after incomplete or marginal excision compared with wide excision, but even without wide excision there may be no recurrence. Abdominal wall reconstruction with polypropylene mesh, polytetrafluoroethylene sheet or a myocutaneous flap may be required[135–137].

Mesenteric desmoids are rarely small enough or sufficiently localized to allow complete excision, and the most frequent site at the root of the small bowel mesentery and intimate relation to the mesenteric vessels means that often a considerable length of small bowel has to be sacrificed[93] when resection is possible. This surgery is hazardous, with a perioperative mortality rate of 10–60 per cent, usually from blood loss[11,12,17,37,138], and a major morbidity rate of 22–60 per cent. Recurrence here is more frequent than at other sites[8,11,20], occurring in 65–88 per cent. Sporadic desmoids and those associated with FAP behave differently, the latter having a higher recurrence rate even if excised completely[33,96]. Partial excision (but not biopsy) may accelerate growth[8]. There have been two reported cases of small bowel transplantation following enterectomy to excise large mesenteric desmoids[139,140]. Most authors[8,95] recommend that surgery should be avoided for mesenteric desmoids because of the risk of accelerated growth and high risk of recurrence. Nevertheless, operation may be needed to bypass bowel obstruction or relieve ureteric obstruction, either with stents or by ureteroureterostomy[17].

Radiotherapy

Radiotherapy by various techniques has been used; a total dose of 50–60 Gy by external-beam interoperative treatment[141] or brachytherapy[142,143] have yielded similar results. Radiotherapy was used primarily to avoid mutilating surgery, but more recently it has been employed as an adjunct to surgery when excision is incomplete or when recurrent disease has been resected. There is evidence that this may reduce recurrence rates both at extra-abdominal sites[19,134,144–147] and in the abdominal wall[148,149]. Recurrence rates of 40–70 per cent after surgery alone are reported to drop to 20–40 per cent when radiotherapy is added, leading some authors[38,144] to recommend its routine use when anything less than a wide excision is performed. Treatment with radiotherapy alone has been associated with local control rates similar to those after surgery alone[147], but tumour regression can be slow.

Intra-abdominal desmoids treated by radiotherapy behave differently, either not responding[11,37,150], or increasing in size[9], or showing a higher recurrence rate after adjuvant radiotherapy than after surgery alone[49] Furthermore, the use of radiotherapy at this site is limited by radiosensitivity of surrounding intra-abdominal structures. Nevertheless, a handful of patients have been treated with some success[134,142,151–153]. Intra-abdominal desmoids may be less radiosensitive than those at other sites and any effect of radiotherapy may possibly be a byproduct of ovarian irradiation[3], explaining the better results in women than men in some reports[14,32].

Pharmacological treatment

Various medical treatments have been reported to give mixed success. Non-steroidal anti-inflammatory drugs (NSAIDs) and antioestrogens are the most frequently employed and most widely documented, but other modifiers of adenosine 3′,5′-cyclic monophosphate (cAMP) metabolism, corticosteroids, colchicine, interferon α, interleukin 2 and warfarin have all been used. There have been reports of desmoid regression, sometimes dramatic, associated with some of these, but none is predictably efficacious and there are almost as many reports of failure as of success. There have been no prospective randomized trials and it is difficult to assess the value of different drugs because of the small numbers in each study. Again sporadic and FAP-associated desmoids, and tumours at different sites, are often reported together. This, coupled with the fact that drugs are often used in combination, can make the interpretation of results difficult.

Sulindac and indomethacin are the NSAIDs that have been used. They inhibit prostaglandin synthesis, which is thought to promote immunological attack on tumour cells, and also inhibit ornithine decarboxylase, an enzyme associated with tumour proliferation. In addition, they are known to cause a decrease in cAMP concentrations in tumour cells, which can lead to interruption of the cell cycle. There is evidence that NSAIDs can reduce tumour growth in experimental models[154] and polyp numbers in the rectal stump of patients with FAP following ileorectal anastomosis. Overall, the studies of NSAIDs alone[98,155,156] show an objective response rate of about 50 per cent (*Table 1*). There are also reports of their use in combination with antioestrogen[8,98,155,156] or ascorbic acid[157]. Most responses occurred at from 2 weeks to 3 months of treatment, but some were observed up to 2 years after the start of therapy. In a retrospective controlled study Tsukada *et al.*[98] showed significant benefit from tamoxifen, sulindac or indomethacin, alone or in combination, compared with controls not given any drug treatment, and of sulindac alone compared with these other drugs. There is evidence that sulindac, in particular, can be effective and, as NSAIDs are relatively non-toxic, it is often used as a first-line treatment.

Antioestrogens were used in logical response to the observations of the influence of sex hormones on desmoid growth. Some success has been achieved with progestogens, such as medroxyprogesterone acetate[158], and goserelin has also been used[159]. Testosterone use has shown no benefit[99]. Most attention has focused on the triphenylethylene, tamoxifen[32], and its chlorinated analogue, toremifene.

Oestrogen receptor blockade restricts RNA synthesis and alters the transcription of genes involved in tumour growth. However, not all desmoids are oestrogen receptor positive and, as is the case in carcinoma of the breast, alternative mechanisms of action have been suggested. Tamoxifen has an effect on prostaglandin metabolism and may also act via stromal–epithelial interactions[160], inducing transforming growth factor β production in stromal fibroblasts, which inhibits fibroblast growth *in*

Table 1 Treatment with non-steroidal anti-inflammatory drugs of intra-abdominal desmoids in patients with familial adenomatous polyposis

			Outcome			
Reference	No of patients	Drug	Complete regression	Partial regression	Static	Progression
Klein *et al.*[156]	2	Indomethacin	0	0	0	2
Tsukada *et al.*[98]	14	Sulindac	1	7	4	2
	4	Indomethacin	1	0	1	2
Waddell and Kirsch[155]	4	Sulindac	0	2	1	1
Total	24		2	9	6	7

Table 2 Treatment with antioestrogens of intra-abdominal desmoids in patients with familial adenomatous polyposis

			Outcome			
Reference	No. of patients	Drug	Complete regression	Partial regression	Static	Progression
Brooks *et al.*[51]	9F, 3M	Toremifene	1	5	3	3
Tsukada *et al*[98]	3F	Tamoxifen	0	1	1	1
Total	15		1	6	4	4

vitro[161]. Antioestrogen binding sites distinct from oestrogen receptors have been identified in 79 per cent of desmoids[45].

Most patients treated with tamoxifen or toremifene have been women, who were often given NSAIDs or other treatments in addition[32,35,51,156,162–164]. Taken together, the studies (*Table 2*) show an objective response rate of about 50 per cent when treating intra-abdominal desmoids in FAP with antioestrogens alone[51,155]. Response can be variable, even between different tumours in the same patient, and the initial response occurs between 2 weeks and 6 months after the start of treatment.

Theophylline, testolactone and chlorothiazide synergize the action of adenosine 3′,5′-monophosphate and may inhibit adenosine 3′,5′-monophosphate diesterase[31]. This causes a rise in intracellular cAMP levels and has been shown to differentiate Chinese hamster ovary cells to mature fibroblasts *in vitro*. There have been a few reports of the use of these drugs to treat desmoids, with mixed results[8,31,33,165]. Ascorbic acid, which causes a fall in intracellular cAMP concentration, has also been used in a few patients, particularly in combination with NSAIDs[157]. Again, the results are mixed and on the whole unconvincing.

Glucocorticoids inhibit growth of desmoid fibroblasts in culture[166] and have been effective clinically in a few cases[167,168]. Colchicine disrupts microtubules, causing a decrease in intracellular collagen formation. It is used in the management of palmar and penile fibromatosis and there is a single report of its use in sporadic extra-abdominal desmoid disease, with good result[169]. Warfarin[155] and interleukin 2[170] have been tried with little benefit, but a single case report[171] of treatment with interferon α, which inhibits fibroblasts and stimulates collagenase *in vitro* and is used to treat keloids and systemic sclerosis, was promising.

Cytotoxic chemotherapy

Cytotoxic chemotherapy was originally used as a last resort in recurrent, irresectable or aggressive desmoid disease because of the similarities between this and low-grade fibrosarcoma. In general, objective remissions of variable degree and duration have been noted with almost all agents, including actinomycin D, cyclophosphamide and vincristine[172], actinomycin D, vinblastine and methotrexate[173,174] and others[9,52,144], but the numbers reported are small.

There is increasing evidence that the antisarcoma regimen consisting of doxorubicin and dacarbazine is effective in the treatment of life-threatening intra-abdominal desmoid disease in FAP. Nine cases have been reported (*Table 3*)[111,175,176], with complete tumour regression in four and partial regression in five. In another case doxorubicin was used alone, with subsequent partial tumour regression[170]. These results have prompted the authors of the most recent report to recommend that this treatment should be considered for patients with FAP with symptomatic irresectable desmoid that is unresponsive to conventional medical therapy, and to suggest that it be used at an earlier stage in the management of such patients.

Treatment recommendations

Desmoids are pathologically benign, have a variable growth rate, and occasional examples of spontaneous regression have occurred. Surgery carries considerable risks in intra-abdominal disease and there is a lack of consistently effective alternatives. There is, however, substantial mortality and morbidity associated with desmoid tumours. Despite the fact that doxorubicin and dacarbazine are potentially toxic, they should be considered in some cases of clinically aggressive disease.

The treatment protocol developed at St Mark's Hospital after a comprehensive review of the literature recommends imaging by CT and initial treatment with sulindac 150 mg twice daily for 6 months. If growth continues, toremifene 180 mg daily is added. If the desmoid is still growing or is giving rise to significant symptoms after a further 6 months, MRI is performed to assess tumour cellularity, and doxorubicin and

Table 3 Doxorubicin and dacarbazine chemotherapy for intra-abdominal desmoids in patients with familial adenomatous polyposis

Reference	Centre	No. of patients	Failed prior treatment	Treatment regimen	Adverse effects	Outcome	
						Complete regression	Partial regression
Hamilton *et al.*[175]	Toronto	3	Sulindac (3 patients) Tamoxifen (3 patients) Toremifene	Doxorubicin and dacarbazine (7 cycles), then carboplatin and dacarbazine	Febrile neutropenia (2 patients)	0	3
Lynch *et al.*[111]	Omaha, Nebraska	2	Sulindac Tamoxifen (2 patients) Partial resection Radiotherapy vincristine cyclophosphamide, azathioprine and prednisolone	Doxorubicin and dacarbazine (5–7 cycles), then carboplatin and dacarbazine	Cardiotoxicity (1 patient)	2	0
Patel *et al.*[176]	Houston, Texas	4	Partial resection (3 patients) Complete resection Tamoxifen	Doxorubicin and dacarbazine (8–10 cycles) and cyclophosphamide (1 patient), then ifosfamide (1 patient)	Probable cardiotoxicity (1 patient, who died)	2	2
Seiter and Kemeny[170]	New York	1	Resection (×3) Indomethacin Tamoxifen Interleukin 2	Doxorubicin	Febrile neutropenia (1 patient)	1	0
Total		10			Febrile neutropenia (3 patients) Cardiotoxicity (2 patients; 1 died)	5	5

dacarbazine chemotherapy considered. Any patient presenting with a rapidly growing or severely symptomatic desmoid is started on both sulindac and toremifene at the above doses, and cytotoxic chemotherapy is considered immediately. Once a desmoid has stabilized or regressed, the doses of sulindac or toremifene can be reduced cautiously. If a desmoid is found at surgery that can be resected with a minimum of small bowel, this should be done. Otherwise, surgery is reserved for obstructive complications and abdominal wall desmoids.

Conclusions

Desmoid tumours, particularly when intra-abdominal, are a serious and increasing problem in patients with FAP. It is not known whether they are, indeed, true neoplasms or the result of a generalized fibroblast abnormality; there is increasing evidence to support the former. Further study of the underlying genetics and molecular biology of desmoids may allow the identification of patients who are at particular risk of their development. This raises the prospect of modifying the management of this group, perhaps delaying colectomy slightly, employing minimally invasive techniques to reduce surgical trauma or opting for primary restorative proctocolectomy to avoid subsequent surgery. Recognition of high-risk patients may justify clinical trials of perioperative prophylaxis.

It has been proposed that the incidence of intra-abdominal desmoids may have been underestimated, as some never progress to become symptomatic[8]. It is known that desmoids are more likely to recur after surgery if large[2], and it has been suggested that treatment may be more effective when the tumour burden is small[156]. More intensive screening of those with FAP for intra-abdominal desmoid disease would establish the true incidence, improve knowledge of the natural history and allow early treatment. Although desmoid disease can run a severe course, prolonged periods of stability and even regression have been reported. There is a need to identify the minority of desmoids that grow rapidly, so that they can be treated aggressively. MRI may offer some prognostic information and may also be valuable in monitoring response to treatment. Finally, further studies of the treatment of intra-abdominal desmoids in patients with FAP are required to establish optimal protocols. These studies will probably need to involve several centres in order to overcome the problems caused by the rarity of this condition.

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British Journal of Surgery 1996, 83, 1505–1511

Review

Abdominal wounds in war

R. COUPLAND

Medical Division, The International Committee of the Red Cross, 19 Avenue de la Paix, CH 1202 Geneva, Switzerland
Correspondence to: Mr R. Coupland

The reported mortality rate associated with abdominal wounds sustained in war varies considerably because of the heterogeneity of wounds and the different circumstances under which figures have been collected rather than different treatment strategies. This review draws together a personal experience, reports from ten wars, and information from a database for war wounded into an analysis of abdominal wounds. The analysis attempts to bring understanding to why people die with abdominal wounds in war and so clarifies logistic and treatment issues.

Abdominal wounds caused by missiles during armed conflict are common and life threatening. They are the wounds for which surgery has the greatest impact on overall survival[1]. They carry a potentially high mortality rate if not treated or if treated incorrectly, and a normal life is possible for the majority of survivors. The factors that determine mortality from abdominal wounds in war are complex and difficult to quantify. Reported figures vary considerably; one reason is that they have been collected under different circumstances. The arrival of many casualties, delay before reaching a surgical facility and lack of surgical resource or expertise are factors that increase mortality; only tangential reference is made to them. There is no universally accepted quantification of injury severity. The result is that operative strategies, especially colostomy, have assumed great importance.

My experience with abdominal war wounds has been gained in nine countries in the Middle East, Africa and Asia where hospitals have been established by the International Committee of the Red Cross (ICRC) to treat the war wounded. In these hospitals, general surgeons work with a basic level of technology (by policy) and without onward referral to specialized colleagues. The wounded tend to arrive within 24 h of injury but only about one-quarter arrive within 6 h; approximately 10 per cent require laparotomy[2,3]. The majority with abdominal wounds arrive in a good general condition with a systolic blood pressure of over 100 mmHg. At laparotomy there is always some blood in the abdominal cavity but active bleeding is found rarely, even from hepatic wounds. Life is usually threatened by intestinal perforations alone and in such situations there is a good chance of survival (*Fig. 1*). However, armed banditry and changes in political or military circumstances may mean that the wounded arrive at hospital within minutes of injury and in such cases another form of abdominal trauma is seen. Casualties may have large abdominal wounds, often with evisceration, active bleeding and multiple organ injury (*Fig. 2*); they arrive hypovolaemic and in poor general condition. Nevertheless, they are a minority of those with abdominal wounds. Close-range shotgun wounds are the civilian equivalent[4]. In my hands, in the context of an ICRC hospital and despite urgent operation, most people with these severe abdominal injuries die on the operating table or shortly after surgery. Haemorrhage may be controlled but repair of the associated intestinal, hepatic or vascular wounds may not be possible. There may be more than one missile track and there are frequently wounds in other regions. Successful treatment of severe abdominal wounds

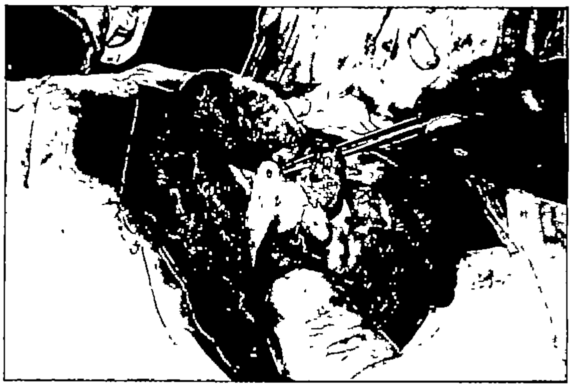

Fig. 1 Laparotomy in a patient wounded by a hand grenade more than 24 h previously. The only visceral wound was perforation of the small intestine by a metallic fragment (shown) Fibrinous exudate is visible on the other loops of intestine. The perforations were sutured and recovery was uneventful

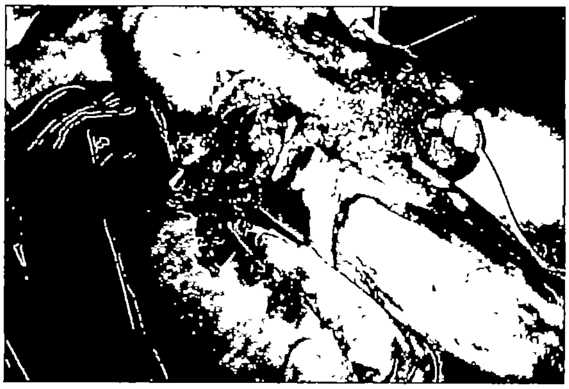

Fig. 2 Missile wound of the abdomen. The patient's general condition was poor on admission, with a systolic blood pressure of 70 mmHg. Apart from evisceration, he had multiple perforations of the small and large intestines with iliac vessel injury. Despite urgent surgery he died on the operating table. One factor contributing to death was limited blood for transfusion

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Paper accepted 27 June 1996

requires urgency, a high level of surgical expertise, technological resource and, importantly, an adequate supply of blood for transfusions[5]. Provision of these may be impossible when the fighting is close to the hospital.

Outside the basic but organized facilities in an ICRC hospital, I have witnessed civilian hospitals that were so disrupted by the conflict that the wounded arrived in the operating theatre without assessment, resuscitation or documentation. Anaesthesia was given by an unqualified anaesthetist and those doing the operations were challenged by the most straightforward of procedures. Postoperative care was the responsibility of the friends or relatives of the wounded person. All intravenous fluids, antibiotics, analgesics and their administration had to be bought; they were given for the first time 2 or 3 days after admission, assuming they had been prescribed in the first place. In one such situation, an ICRC medical team was fully occupied in finding and treating unresuscitated people who were about to be operated on or who had recently had operations. The mortality rate from laparotomy before the intervention of our team was certainly near to 100 per cent whether or not there was intra-abdominal injury. With non-operative management at least 20 per cent could have survived[1,6,7].

In some countries, senior military surgeons have the attitude that front-line surgery is good experience for 'the young surgeons'. In one such country, a 'young surgeon' informed me that the situation at the front-line hospital was dangerous and chaotic. He and his colleagues were expected to operate on all casualties and so they were opening the abdomen of soldiers with abdominal wounds on the slightest pretence, under ketamine anaesthesia, and after a minimal intervention simply closing them again. They hoped more competent care would be reached later. Criticism by their seniors and other soldiers for not working was thus avoided. When duty surgeon in the ICRC hospitals, I have admitted many people who have had a front-line laparotomy. They usually arrive dehydrated with pus, faeces, urine or bile leaking from wounds, incisions or drain sites (*Fig. 3*); there is rarely any clinical record. After rehydration, antibiotics and correction of anaemia, a second laparotomy reveals missed perforations, leaking anastomoses or repairs, and retained surgical compresses. The associated mortality rate is so high that it is difficult to know whether a second operation has any benefit over conservative management. The fact that both the extent of injury and the operation performed are unknown makes this a difficult clinical decision for the receiving surgeon. I am sure that these patients would have fared better with front-line resuscitation only and immediate transfer to the ICRC hospital.

Although critical of this surgical practice, I should point out that I have been placed in situations where fatigue, fear for my own safety and disruption of the organized hospital infrastructure by the conflict may have rendered my own practice unsafe and unsound. This is the reality of war. It underlines the importance of correct first aid and transportation of the wounded to an organized, competent and reasonably secure surgical facility. In the light of such experience, this paper reviews data from World War II, nine more recent conflicts, urban bullet wounds from South Africa and the USA, and figures from the wound database of the ICRC. It is an attempt to quantify the factors influencing mortality from abdominal wounds, taking account also of the impact of the constraints that arrive with war.

Fig. 3 Admission photograph of a patient who had had a field laparotomy 48 h previously. There was no accompanying information. His general condition was poor; pulse rate was 120 per min and systolic blood pressure was 100 mmHg. The fluid draining from the small tube drain smelled of faeces, the bullet entry wound on the left side of the abdomen had been sutured It was decided further laparotomy was indicated. A sutured perforation of the small intestine and open perforation of the rectosigmoid junction were found and a colostomy was performed. The abdomen was closed with difficulty because of necrotic tissue in the previous surgical wound The patient died 24 h after operation

Review of the literature

The reported mortality rate from abdominal wounds in recent wars or civilian series of gunshot wounds is shown in *Table 1*[2,3,8–21] and for treated patients varies between 3 and 31·4 per cent; there is no uniformity of data collection. Figures may relate to all abdominal casualties[13,20], only those who reach hospital alive[3,12,15], those who have a wound of the abdominal region[12,20] or only those who have a laparotomy[2,3,8–21]. Some reports are small series[2,3,8,11,14]. In addition, the multiplicity of wounds may mean the eventual outcome for a patient is unrelated to his or her abdominal wound or its treatment[12,13,20]. Mortality may increase with a particular cause of injury, for example bomb blast[13]. A long evacuation time may alter in-hospital mortality[1,8,18]. In a triage situation, only those wounded whose lives are salvageable by laparotomy may be registered[14–16,20]. Alternatively, deaths may be registered only in the early phase because of onward evacuation of the wounded to other facilities[12,16].

Some references acknowledge the heterogeneity of abdominal wounds and the implication for mortality. Rozin and Kleinman[15] judged that 21 per cent of people required operation before evacuation to a base hospital because of severe abdominal injury, as indicated by hypovolaemia and large abdominal wounds; the eventual mortality rate was 18·9 per cent. Other reports associate a high mortality rate with hypovolaemia on admission[19,22]. Whatever the organ injured, if it is injured in isolation there is a lower mortality rate; understandably, the rate rises with the number of organs injured[2,8,9,12,18–20,22]. This is better documented and quantified in civilian gunshot series[6,7,17]. Where the main cause of injury was handgun bullets, Feliciano *et al.*[17] found that 25 per cent of abdominal gunshot wounds affected major abdominal vessels and carried a mortality rate of 39·2 per cent, while Collins *et al.*[23] reported a rate for such injury of 22·2 per cent. In war, these injuries are reported to carry a mortality rate near to 100 per cent[2,10,13]; however, some authors have not referred to this as part of laparotomy

Table 1 Mortality from abdominal wounds and/or laparotomy from wars

Reference	Year	Conflict or country	Total no. of casualties	No in series	Mortality rate (%)	Comment
Ogilvie[8]	1944	World War II	—	628	39·2	Forward surgery but follow-up deaths recorded
Imes[9]	1945	World War II	—	358	20·1	Penicillin available Possibly first reported series
Jones *et al*[10]	1968	Vietnam	1011	158	—	158 laparotomies Improved mortality claimed No figures given
Xeros and Symeonides[11]	1976	Cyprus	—	80	14	General hospital care
Hardaway[12]	1978	Vietnam	17726	1350	4·5	(i) 2454 'abdominal wounds' but only 1350 laparotomies. (ii) Deaths recorded only before evacuation from Vietnam
Owen-Smith[13]	1981	Northern Ireland	2000	267	41·2	All abdominal wounded including those dead on arrival at hospital
				51	31	Mortality after laparotomy (values include 33 per cent bomb blast)
Jackson *et al.*[14]	1983	Falkland	233	30	3	Mortality from laparotomy Forward surgical team
Trouwburst *et al*[3]	1987	Afghanistan	1033	—	25·6	Not clear whether mortality from all abdominal wounds, laparotomy only or whether thoracoabdominal wounds are also included (ICRC hospital providing definitive care)
Rozin and Kleinman[15]	1987	Arab–Israeli	40000	178	7·9	All those with abdominal wounds operated on
				141	5·0	Operated on in rear hospital
				37	19	Operated on in evacuation hospital
Fosse *et al*[16]	1988	Lebanon	1500	24	5	Patients transferred within 7 days
Feliciano *et al.*[17]	1988	USA	—	300	11·7	Civilian series, mostly hand-guns; operated on
				226	2·7	With no intra-abdominal vascular injury
				74	39	With intra-abdominal vascular injury
Dumurgier and Jancovici[18]	1989	Chad	—	505	29·0	All laparotomies. Long evacuation to hospital. No blood transfusion possible
Nassoura *et al.*[19]	1991	Lebanon	30000	1314(?)	9·5	Mortality rate from laparotomy '9·5 per cent gunshot wounds' (of 1314 or 706, not clear in text)
				—	2·8	Patients with systolic blood pressure greater than 90 mmHg
				—	26·5	Patients with systolic blood pressure less than 90 mmHg
				—	4·4	With abdominal injury only
				—	14·4	Combined with extra-abdominal injury
Morris and Sugrue[2]	1991	Afghanistan	650	70	13	All patients having laparotomy (ICRC hospital providing definitive care)
Rignault[20]	1992 (quoting)	World War I	—	—	53	Total mortality from abdominal wounds
		World War II	—	—	18–36	Total mortality from abdominal wounds
		Vietnam	6000	476	37·2	Total mortality from abdominal wounds
				338	11·5	Hospital mortality with abdominal wounds (13·5 per cent including negative laparotomy)
				265	9·4	Hospital mortality with primary abdominal wound
				73	19	Hospital mortality from multiple wounds including abdomen
Cuk *et al*[21]	1994	Former Yugoslavia	4292	156	4·5	Primary management in base hospital
				254	14·9	Primary management elsewhere and then transfer to base hospital

ICRC, International Committee of the Red Cross

findings[8,9,12]. The extent of tissue damage along the abdominal track of the missile is important[2,9,10,13,15,18,20], but this has been neither quantified nor interpreted in terms of energy transfer from missile to abdominal organs. However, surgeons do recognize the surgical implications in terms of greater tissue damage in wounds of the liver and colon[2,8,9,18,24–35]. The extent of damage to different organs has been quantified in penetrating abdominal trauma in a civilian setting, but this has been linked only to subsequent complications and not to mortality[36].

The review permits recognition of the elements of severe penetrating abdominal trauma in war. However, the factors responsible for mortality have not been quantified.

Data from the ICRC wound database

The ICRC wound database carries basic information on 25189 war-wounded persons admitted to ICRC hospitals in five different locations; 7479 had wounds scored by the Red Cross wound classification. This classification is a system whereby any wound from any weapon is categorized according to the extent of tissue damage and the structures injured. It is designed as a quick and simple means of gathering data from the field[37–43]. Each wound is given a score according to the size of the skin wound(s), the presence of a cavity in the wound (for abdominal wounds this is indicated by whether the wound in the abdominal wall admits two fingers), whether there is a fracture, whether there has been 'vital injury' (for abdominal wounds this is indicated by breach of the peritoneum or organ injury) and whether there are metallic bodies on radiography. From the score, the wound may be graded according to size (grade 1, small penetrating wounds; grade 2, wounds with a cavity but skin wounds measuring less than 10 cm; grade 3, wounds with a cavity and skin wounds measuring 10 cm or more) and typed according to structures injured (type ST, soft tissue only; type F, fracture; type V, vital injury; type VF, vital injury and fracture). Thus any wound falls into one of the 12 categories shown in *Table 2*.

There is a total of 1148 persons with abdominal wounds and 617 with wounds of the buttocks or pelvis; those with multiple regions wounded are included. Of these, 335 had only abdominal wounds and 195 had only pelvic wounds; those with multiple regions wounded are excluded in the following analysis. *Table 2* shows the different categories into which the isolated wounds of these 530 persons fall, along with the number who died with each category of wound. Of the 530 wounds, 257 (48·5 per cent) did not have a V component, i.e. there was neither peritoneal perforation nor organ injury. Among the 167 people with grade 1 wounds with a V component there were 11 deaths (6·6 per cent mortality rate); among the 106 with grade 2 and 3 wounds with a V component there were 15 deaths (14·2 per cent mortality rate). This difference is statistically significant ($\chi^2 = 4{\cdot}31$, $P < 0{\cdot}05$). The absence of mortality in the 11 who had a grade 3 wound with a V component is explained by the fact that those with such large skin wounds of the abdominal wall survived only because the track of the missile was tangential and therefore did not deliver much of its energy to the abdominal contents. Most casualties with grade 3 abdominal wounds and in whom the track of the missile(s) involved the abdominal cavity die before reaching hospital.

The literature review combined with these ICRC data shows that mortality is related to the number of organs injured, extent of organ injury, blood loss (as indicated by hypovolaemia) and energy transfer from the missile to the tissues (as indicated by the size of the wound in the abdominal wall). How these interplay in the face of variable standards of treatment remains unclear.

Table 2 Categorization by the Red Cross wound classification of wounds in 530 patients who had only one regional wound recorded of either the abdomen or pelvis

Type	Grade 1	Grade 2	Grade 3
ST	126	87	4
F	15	21	4
V	143 (10)	64 (10)	5
VF	24 (1)	31 (5)	6

Numbers in parentheses are those who died; figures are from the International Committee of the Red Cross database. Grade 1, skin wounds less than 10 cm without cavity; grade 2, skin wounds less than 10 cm with cavity; grade 3, skin wounds 10 cm or more with cavity; type ST, soft tissue wound only; type F, wound with fracture, type V, wound with vital injury; type VF, wound with vital injury and fracture

Ballistic analysis

Larger wounds are caused by greater energy transfer from missile to tissue. The two clinical pictures of abdominal wounds seen in the field and their different associated mortality can be explained in these terms. Low energy transfer (LET) results in a narrow wound track and the gravity of the injury is determined by the structures lacerated along this track. As energy transfer increases, the wound track becomes larger and there is a greater chance of peritoneal perforation, multiple organ injury, severe organ injury and major vessel injury; the chance of these components of severe injury occurring in combination also increases. The place of temporary cavitation and shock waves in abdominal wounds has not been established. The transition from LET wounds to the clinical picture of the severe high energy transfer (HET) wounds occurs with a small rise in energy transfer at a critical but undetermined point. However, energy transfer alone does not determine eventual death; the difficulty and urgency of treating HET wounds of the abdomen are additional factors. It seems likely that there exists an exponential component in the relationship between energy transfer to abdominal organs and death rate in treated patients.

Curve A in *Fig. 4* represents mortality with optimal surgical care plotted against transfer of energy within the abdomen. This is arrived at by considering the exponential relationship between death rate and transfer of energy, as outlined above, with two other factors. First, a series of handgun bullets (500 J)[44] gives an overall mortality rate of around 12 per cent in a good surgical facility with rapid access to the patients. Second, even with optimal treatment, few people would survive the transfer of all the energy of an assault rifle bullet within the abdominal cavity or the retroperitoneal structures. Such a bullet imparts between 2000 and 3000 J and the resulting track of permanent damage, if 20 cm long, is about 15 cm in diameter[44]; the extent of tissue damage is most likely irreparable, even if the surgeon succeeds in arresting the haemorrhage. This ballistic analysis is supported in part by the rapidly increasing mortality rate associated with increasing number of organs injured, as reported by Nance *et al.*[6] The shape and position of this hypothetical

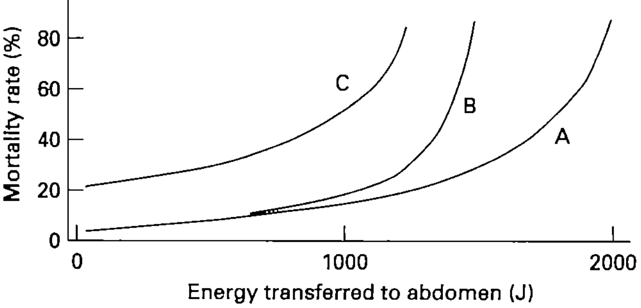

Fig. 4 A hypothetical graph showing energy transfer from missile to abdominal organs plotted against mortality rate for patients with abdominal wounds The significance of curves A, B and C is explained in the text

curve A could be debated; its importance lies in explaining how a linear increase in energy transfer generates two dissimilar clinical groups. Any factors that influence overall mortality from abdominal wounds may be referred to this curve. (If accurate data were ever made available, it is possible that curve A would prove to be part of a sigmoid curve.)

The literature review indicates that the mortality rate associated with LET wounds is about 10 per cent if competent treatment is available. A working value of 50 per cent for the mortality rate from HET wounds with optimal treatment is reasonable if close-range shotgun wounds are considered as equivalent[4,45]. The proportion of people with abdominal wounds who need front-line surgery[15], the proportion of handgun bullet wounds that affect major abdominal vessels[17] and the proportion of abdominal wounds that are grade 2 or 3 with a V component as given by the Red Cross wound classification (*Table 2*) suggest that patients with HET wounds are in the minority. For the purposes of this paper this proportion will be taken as 20 per cent; obviously this will change with each minute added to the time taken to reach hospital.

Constraints imposed by war on optimal management of abdominal wounds

The ballistic analysis permits quantification of the impact on mortality of constraints such as a delay before surgery, insufficient resource or lack of surgical and anaesthetic competence. A competent surgical facility with adequate resource and early access to the wounded, which can provide optimal care, would generate curve A in *Fig. 4*. This should represent the objective of modern military surgical care. However, if the wounded receive competent treatment but after a delay of hours, the 20 per cent with severe wounds die before reaching surgical treatment; this is represented by curve B and would be generated in the context of an ICRC hospital with more difficult access to the wounded and fewer resources. However, if the hospital is undersupplied, overwhelmed and the medical personnel are tired, untrained or frightened, neither competent surgical care nor safe anaesthetic practice is likely. Those with HET wounds are lost anyway and, importantly, the mortality rate of the majority with LET wounds rises, as represented by curve C.

If, with treatment available, the mortality rate from HET abdominal wounds is 50 per cent (which is a generous estimate), total lives lost in the different situations can be calculated. In the situation represented by curve A, for every 100 patients with abdominal wounds, ten lives are saved in those with HET wounds in addition to the 72 (90 per cent) of the 80 lives saved in those with simple wounds. In the situation represented by curve B, only the 72 lives of those with LET wounds would be saved; those with HET wounds would die before reaching hospital. Paradoxically, hospital mortality is lower in the situation represented by curve B. If the constraints also cause the mortality rate of those with LET wounds to rise from 10 to 20 per cent, as represented by curve C, by the same calculation only 64 lives per 100 would be saved. This model demonstrates that those with LET abdominal wounds must not be denied competent surgical care by focusing all surgical time, energy and resource on those with HET wounds. A relatively small rise in the mortality rate of the majority with LET wounds outweighs any spectacular successes within the minority with HET wounds. If curve A is obviously not achievable, the mortality rate associated with curve B should be accepted. Disagreement with the above figures based on different estimates is certain; it should be considered as a first attempt to rationalize a complex subject. Whatever else, the existence of a recognizable minority with HET wounds with specific clinical and logistic implications cannot be denied.

A selective conservative approach to abdominal wounds, requiring refined judgement[6,7], has not been evaluated in war and is unlikely to be. But approximately one-quarter of patients with handgun bullet wounds would survive without laparotomy[6,7,46], and nearly half of the war wounds of the abdominal region neither penetrate the peritoneal cavity nor cause serious injury, as shown in *Table 2*. Anecdotally, some patients with intestinal perforation from war wounds survive without surgery[1,8]. Therefore, as represented by curve C, an increased mortality rate associated with laparotomy for LET wounds under front-line conditions has serious implications, because of the significant proportion of people who do not need to be exposed to that risk for their survival. Surgical judgement is required to identify not only those who need urgent operation but also those who do not need laparotomy at all; this judgement may not be available in the chaos of the front-line hospital.

Other constraints have been reported that are referrable to this model. Two military authors acknowledge that providing rapid first aid and evacuation to a surgical hospital is difficult, if not impossible, when the force concerned is in retreat[47,48]. Transporting the wounded after laparotomy is associated with a high mortality rate[8,15,21,22,49]. This may represent a combination of operations performed under front-line conditions for more severe injury, transport in the early postoperative period, disruption of immediate postoperative care, or a combination of these. Potent influences on surgical judgement and competence are human constraints such as training, food, sleep and security[8,15,25]. Only two papers, both of which report a low mortality rate, refer to the seniority of the front-line surgeons[14,15]. Blood for transfusion is a particularly important resource for treating HET abdominal wounds; this is usually unlimited in a military situation and may be so in a non-military situation[19,50]. In other situations the volume of safe blood may be limited[2,5,18]. Whatever the constraint, those with HET wounds are the most susceptible; by accepting the mortality rate associated with curve B, that associated with curve C can be avoided.

Colonic wounds: the debate

Ogilvie[8] is frequently quoted as proving that death from colonic wounds was reduced as a result of mandatory colostomy. Although he strongly recommended colostomy for all colonic wounds, the small colonic wounds in his series that were closed primarily were associated with a lower mortality rate than others. Many authors have since recommended primary closure of small wounds. Exteriorization, resection or repair with colostomy has been reserved for larger wounds with faecal soiling and/or injury to other organs, especially when the general condition of the patient is poor[2,25-28]. This policy is supported by data from civilian practice[29-33]. Two reports support primary closure or anastomosis without selection of those with smaller wounds[51,52]. There are no mortality figures that support mandatory colostomy for all wounds of the colon. Surgeons should not get caught in the trap of categorizing wounds by weapon or presumed velocity of the missile[34,35,53]. In addition, the need for a second operation to close the colostomy is a significant factor, especially in a developing country at war where this may not be done safely. These arguments do not apply to the protection of repaired rectal wounds with a proximal colostomy; all authors agree on this.

The ballistic analysis of abdominal wounds applies here also. LET wounds affecting the colon are unlikely to be associated with extensive intra-abdominal damage and hypovolaemia, and so the simpler and safer surgical option may be to repair such wounds. By contrast, the simpler and safer operation for colonic injury associated with HET may be to resect the damaged colon and bring out a colostomy or to exteriorize the injury. In HET wounds, some of the viable intestine remaining might nevertheless have the integrity of its 'gut barrier' breached; in combination with haemorrhagic shock, this has implications for the absorption of endotoxins and later multiple organ failure[54]. In the face of the several factors related to energy transfer, it is unlikely that mortality is affected by the choice of operation, assuming a proper level of judgement, experience and competence.

Conclusions and recommendations

Assuming competent surgical care, energy transfer from the missile to tissue is the most important factor determining the mortality associated with abdominal wounds in war. Those with HET wounds of the abdomen are identifiable before operation by the likely direction of the missile track, the size of the wound in the abdominal wall and low systolic blood pressure on admission. They require greater urgency, judgement, expertise and resources, and inevitably have a high mortality rate. Their successful treatment is easily made impossible by the constraints imposed by war.

A well organized military medical service should ensure that those wounded with a genuine need for urgent laparotomy because of bleeding and who would die within hours can, first, have immediate access to a competent and fully supported surgical facility and, second, be evacuated safely[15]. A 'damage control' philosophy[55] may apply to the minority of wounded and presumes that the patient will reach more competent care later. The majority with LET wounds and without signs of bleeding should be given intravenous fluids, antibiotics and analgesia; they will tolerate the transport to a more secure and competent surgical environment. Outside a conventional military context, the focus of surgical resource and competence should always be on the majority with intestinal perforation only, who need surgery to save life but not necessarily on an urgent basis and who have a good chance of survival. The desire to provide urgent surgery must not preclude competent surgical care. Whatever the circumstances, inexperienced and under-equipped surgeons should not attempt the most difficult surgical tasks under the most difficult conditions.

The reality of modern wars must be acknowledged: civilian casualties predominate. Military forces are likely to be used in a United Nations context and the wounded cannot travel along a conventional chain of evacuation. Military doctors may have difficulty accepting that optimal care may not reach the minority with severe wounds[56]. This approach also questions the value of telesurgery for the war wounded, which is often portrayed as laparoscopic surgery performed by robots[57]. To make the claim that deployment of this technology at the front line saves the lives of soldiers with abdominal wounds requires that it be shown to work successfully in the minority with HET wounds, for whom the judgement and operative expertise required are far beyond those needed for performing intestinal repair or resection and anastomosis.

A surgeon receiving wounded who have had a front-line laparotomy where the level of surgical competence or ethics is in doubt should seriously consider a routine 'second-look' laparotomy. This may prevent death for those who have been subjected to an incompetent laparotomy and who have not yet become seriously ill through prolonged sepsis. This does not help with the management of patients who arrive already septic and with evident intestinal leakage after front-line surgery. This review may help avoid this situation.

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British Journal of Surgery 1996, 83, 1512–1516

Laparoscopic ultrasonography during cholecystectomy

M. A. RÖTHLIN, O. SCHOB, R. SCHLUMPF and F. LARGIADÈR

Department of Surgery, Zürich University Hospital, Ramistrasse 100, 8091 Zurich, Switzerland
Correspondence to: PD Dr M. A. Röthlin

The routine use of intraoperative cholangiography during cholecystectomy has been debated extensively. Intraoperative ultrasonography was a quick, efficient alternative in open cholecystectomy. A prospective controlled trial to evaluate its usefulness in laparoscopic cholecystectomy is reported. Two groups of 100 patients each were examined during operation with laparoscopic ultrasonography and intraoperative cholangiography. In the first group an adapted urethral probe was used and in the second group a new specialized laparoscopic probe. Intraoperative cholangiography followed immediately after laparoscopic ultrasonography in each patient. In group 1 bile duct stones ($n = 4$) were detected with a sensitivity of 100 and 75 per cent, a specificity of 98 and 99 per cent, and an overall accuracy of 98 per cent for both ultrasonography and cholangiography. In group 2, 11 patients demonstrated common duct calculi. The sensitivity, specificity and overall accuracy for laparoscopic ultrasonography and intraoperative cholangiography were 91 and 64 per cent, 100 and 100 per cent, and 99 and 96 per cent respectively. The differences between groups 1 and 2 and between ultrasonography and cholangiography were not significant. Variations in the anatomy of the bile duct were observed in 21 patients in group 1 by laparoscopic ultrasonography and in 20 by intraoperative cholangiography. In group 2, 64 variations were demonstrated in 50 individuals by ultrasonography and 61 variations in 47 patients by cholangiography. Vascular variations were seen with ultrasonography in 22 and 24 patients in groups 1 and 2 respectively. In conclusion, laparoscopic ultrasonography (with either probe) proved as accurate as intraoperative cholangiography in detecting bile duct stones, and the specialized probe detected significantly more variations of the bile duct than the adapted probe.

The value of intraoperative cholangiography has been debated for years[1,2]. The introduction of laparoscopic cholecystectomy resulted in a short lull in the debate, which was soon recommenced with renewed vigour[1–5].

In the 1980s a few trials were held to test intraoperative ultrasonography against intraoperative cholangiography in open cholecystectomy[6–8]. The results of both techniques were similar, but intraoperative ultrasonography was never widely used in this context. The main issue at open cholecystectomy was the detection of common duct stones, whereas visualization of anatomical variations of both bile ducts and hepatic vessels was of greater importance after the change to the laparoscopic approach[4,5].

To evaluate intraoperative laparoscopic ultrasonography and intraoperative cholangiography in the detection of common duct stones and anatomical variations, a prospective controlled study employing both techniques was conducted. At the beginning of the study only an adapted probe was available. A specialized laparoscopic scanner subsequently became available. These scanners are costly and the study aimed to determine whether or not the improved results of a laparoscopic ultrasonography probe justify the additional expense.

Patients and methods

Between 1 January 1992 and 31 January 1993, 100 successive unselected patients undergoing laparoscopic cholecystectomy were entered into group 1 of the study. Five additional patients underwent conversion to open cholecystectomy for bleeding ($n = 3$) or inability of the surgeon to delineate anatomical structures ($n = 2$). Group 2 consisted of 100 patients who underwent laparoscopic cholecystectomy between 1 April 1994 and 30 November 1995. During this time, conversion to open cholecystectomy was necessary in three additional patients for bleeding. Sex, age and indication for the operation in the two groups are given in *Table 1*.

Patients in group 1 were examined with a 5·5-MHz sector scanner with a 360° angle and a mobile ultrasound unit (type 3535; B&K Medical, Nærum, Denmark). The probe (type 1850/8523; B&K Medical) had originally been designed for endoluminal ultrasonography of the urinary tract. Its rigid shaft measured 31 cm in length and 7 mm in diameter. The scanner's optimal working depth lay between 1 and 4 cm and it produced 3·5 pictures per second. A protective tube with a plastic tip (type WA 500; B&K Medical) and an outer diameter of 9·5 mm was constructed to protect the tissue from the rotating probe.

Later a probe specially developed for laparoscopic ultrasonography (type 8555; B&K Medical, Gentofte, Denmark) was employed for group 2. The probe consisted of a curved array scanner with a frequency of 5–7·5 MHz mounted on a rod 43 cm in length and 9·5 mm in diameter. The tip of the scanner could be deflected 90° up and down. In contrast to the adapted probe it was capable of both real-time imaging and colour flow Doppler scanning. Both scanners can be immersed in Gigasept (Schülke and Hays GmbH, Zurich, Switzerland) for sterilization.

Preoperative investigation included the patient's history, physical examination and laboratory tests (haematological data, bilirubin, amylase, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase) as well as abdominal ultrasonography

Table 1 Demographic data of patients in groups 1 and 2

	Group 1	Group 2	*P*
Mean (range) age (years)	52·0 (19–80)	49·8 (17–81)	0·25†
Sex ratio (M:F)	40:60	27:73	0·003*
Indications			
Acute cholecystitis	23	27	0·37*
Acute pancreatitis	7	2	0·06*
Symptomatic gallstones	77	73	0·3*

*Fisher's exact test; †student's *t* test

Paper accepted 28 June 1996

Throughout the study laparoscopic ultrasonography was performed by one surgeon (M.A.R.) exclusively. He had had 14 years' experience with emergency, open intraoperative and interventional ultrasonography. His experience in laparoscopic sonography before the beginning of the study was limited to about 30 cases.

Laparoscopic ultrasonography was performed after dissection of the cystic duct and artery in all patients The technique of the examination and normal anatomy have been described in detail elsewhere[9,10] Briefly, the subhepatic space was flooded with saline solution until the hepatoduodenal ligament had been well covered. The scanner was then introduced through a 10-mm cannula in a left paramedian position. The tip was placed in the hepatic hilum where the examination was started. The shaft of the scanner lay parallel to the ligament and the image showed either a transverse (group 1) or a longitudinal (group 2) section of the structures within the ligament. The scanner was slowly retracted over the ligament as far as the cranial edge of the pancreas where the common bile duct curves to the right. The scanner was then rotated to the right to follow the duct into the head of the pancreas to the papilla of Vater. The probe was then removed, the saline was aspirated and the operation continued. The time taken for laparoscopic ultrasonographic examination was measured from the start of flooding to the removal of the scanner. A diameter of less than 7 mm was considered normal for the common bile duct. A sharp echo with an acoustic shadow, situated in the bile ducts, was considered a positive finding for a bile duct stone. Ultrasonographic findings were recorded immediately after the examination, outside the operating theatre, while intraoperative cholangiography was being performed by the operating surgeon.

A 4-Fr ureteral catheter (Rüsch, Kernen, Germany) was passed through a 14-G intravenous cannula into the abdomen The catheter was inserted into the cystic duct through a lateral incision and fixed with an atraumatic grasper. First 5 ml and then 20 ml of undiluted Urografin (Schering, Berlin, Germany) was injected. Fluoroscopy was performed with a mobile C arm (Siremobil 4E; Siemens, Erlangen, Germany). A diameter of less than 9 mm was considered normal for the common bile duct. A circular filling defect in the bile duct was defined as a positive finding for a bile duct stone. The time taken for intraoperative cholangiography was measured from the incision in the cystic duct to the removal of the C arm Allergy to contrast medium or iodine, as well as pregnancy, were considered contraindications for cholangiography.

Patients in group 1 with suspected common duct stones were subjected to preoperative endoscopic retrograde cholangiopancreatography (ERCP). By the time the second group was examined, however, laparoscopic bile duct exploration was possible and preoperative ERCP was not considered mandatory in patients with suspected stones. Bile duct calculi found during operation were removed either during laparoscopic cholecystectomy (group 2) or by postoperative ERCP (group 1), thus corroborating the intraoperative findings.

Statistical analysis was performed with Statview SE Plus software (Abacus Concepts, Berkeley, California, USA) with the unpaired Student's *t* test, Fisher's exact test or the Mann–Whitney *U* test where applicable.

Results

Laparoscopic ultrasonography was performed successfully in all patients. Intraoperative cholangiography had a success rate of 93 per cent in group 1 and of 90 per cent in group 2 ($P = 0{\cdot}32$). In group 1 cholangiography failed in six patients for technical reasons. In one patient it was not performed because of a history of a severe allergic reaction to contrast medium. In group 2, eight failures of cholangiography were due to technical problems, while two patients had a history of allergic reactions to contrast medium.

Bile duct calculi

Common duct stones were verified during or after operation in four patients in group 1 and in 11 in group 2 ($P = 0{\cdot}02$). Laparoscopic ultrasonography demonstrated all four stones in group 1 and ten of 11 in group 2. Intraoperative cholangiography showed three and seven stones in groups 1 and 2 respectively. In group 1, two false-positive findings occurred at laparoscopic ultrasonography. In one patient this was due to debris in a juxtapapillary diverticulum and in the other a stone seen with both techniques could not be verified at ERCP 2 days after operation and was, therefore, counted as false positive. No false-positive findings occurred in group 2 for either technique. The sensitivity, specificity and overall accuracy resulting from these findings are shown in *Table 2*.

The diameter of the stones ranged from 2 to 7 (mean(s.d.) 3·3(1·6)) mm in group 1 and from 1 to 20 (mean(s.d.) 4·9(4·5)) mm in group 2. In group 1 bile duct dilatation was observed in two of three patients by cholangiography and in all four patients with common duct stones by ultrasonography. Five of seven patients with common duct stones demonstrated by intraoperative cholangiography in group 2 had dilated ducts. In seven of ten patients with a positive finding at laparoscopic ultrasonography the bile ducts were dilated.

Anatomical variation of the bile duct

Variations of the biliary anatomy were demonstrated by laparoscopic ultrasonography in 21 patients in group 1. Intraoperative cholangiography showed anatomical variations in 20 patients in group 1. All variations of the cystohepatic junction visualized by ultrasonography were corroborated by cholangiography, which detected a further case with a junction on the left side of the common bile duct. One patient had an extrahepatic junction of the hepatic ducts, with the cystic duct joining the right hepatic duct, shown by laparoscopic ultrasonography. This variation was subsequently shown by intraoperative cholangiography to be an aberrant hepatic duct joining the cystic duct. Two further patients demonstrated an extrahepatic junction of the left and right hepatic duct on ultrasonography, while the level of the hepatic junction could not be judged by cholangiography because points of reference were missing. Therefore, additional information was contributed by intraoperative cholangiography in two patients, while laparoscopic ultrasonography provided more information in a further two. The variations demonstrated with the two techniques are listed in *Table 3*.

Table 2 Sensitivity, specificity and accuracy of laparoscopic ultrasonography and intraoperative cholangiography in the detection of common duct stones

	Group 1	Group 2
Laparoscopic ultrasonography		
Sensitivity (%)	100	91
Specificity (%)	98	100
Accuracy (%)	98	99
Intraoperative cholangiography		
Sensitivity (%)	75	64
Specificity (%)	99	100
Accuracy (%)	98	96

Table 3 Variation in the anatomy of the bile ducts

	Group 1	Group 2	P*
Low hepatic junction	3	6	0·2
Accessory hepatic duct	0 (+1)	0	1·0
Cystic duct merges left	2 (+1)	4 (+2)	0·31
Dorsal cystic junction	7	29 (+1)	0·0001
Ventral cystic junction	2	2	1·0
Long cystic duct	6	17	0·0001
Short cystic duct	0	2	
High cystic junction	1	4	0·13
Total no. of patients	23	50	0·0001

Values in parentheses are additional cases diagnosed by intraoperative cholangiography alone *Fisher's exact test

Table 4 Variation in the anatomy of the hepatic arteries

	Group 1	Group 2	P*
RHA from SMA	6	12	0·01
RHA crossing ventral	15	5	0·005
Cystic artery crossing ventral	1	4 (+2)	0·13
RHA crosses behind portal vein	0	2	
Two RHAs crossing in front of and behind the hepatic duct	0	1	
Total no. of patients	22	24	0·62

Values in parentheses are additional cases found by dissection during operation. RHA, right hepatic artery; SMA, superior mesenteric artery. *Fisher's exact test.

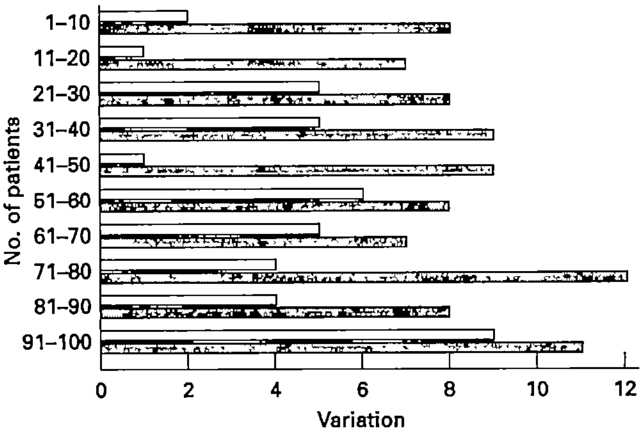

Fig. 1 Learning curve for the detection of anatomical variation: □, group 1; □, group 2

In group 2, 64 anatomical variations of the biliary tree were visualized by laparoscopic ultrasonography in 50 patients Intraoperative cholangiography demonstrated such variations in 61 cases. It provided additional information in three patients (one dorsal junction and two junctions on the left of the hepatic duct). In six patients with an extrahepatic low junction of the hepatic ducts, cholangiography could not corroborate the findings owing to the lack of points of reference. Significantly more anatomical variations of the bile ducts were found in group 2 (*Table 3*). Both dorsal and intrapancreatic cystohepatic junctions were observed significantly more frequently in the second group ($P = 0{\cdot}0001$).

Anatomical variations of the hepatic arteries

Variations of the hepatic arteries were seen in 21 patients in group 1 by laparoscopic ultrasonography only, and in one patient by both ultrasonography and cholangiography (compression of the hepatic duct by a right hepatic artery crossing ventrally). In group 2, 24 cases were detected by laparoscopic ultrasonography. Two additional cases (cystic arteries crossing ventrally) were discovered during further dissection and considered false-negative results. The difference in the number of vascular variations in groups 1 and 2 was not significant ($P = 0{\cdot}62$). The types of variation observed in the two groups are shown in *Table 4*. The number of all anatomical variations detected ultrasonographically in relation to the experience of the observer (learning curve) is demonstrated in *Fig. 1*.

Time required for examination

The time necessary for the laparoscopic ultrasonographic examination in group 1 ranged from 2 to 12 (mean(s.d.) 5·4(2·4)) min. Intraoperative cholangiography was performed in 4–37 (mean(s.d.) 16·4(7·4)) min. The difference was highly significant ($P = 0{\cdot}0001$). In group 2 the time range for laparoscopic ultrasonography was 2–10 (mean(s.d.) 4·5(1·7)) min, while for intraoperative cholangiography it was 7–30 (mean(s.d.) 13·5(4·5)) min. Again, the difference was highly significant ($P = 0{\cdot}0001$).

Discussion

During conventional cholecystectomy intraoperative ultrasonography has been used by only a few groups[6–8]. The results of intraoperative ultrasonography were similar or even better than those for intraoperative cholangiography. The sensitivity and specificity for the detection of bile duct stones ranged from 93 to 96 per cent for intraoperative ultrasonography and from 93 to 99 per cent for intraoperative cholangiography. At the beginning of laparoscopic cholecystectomy, routine intraoperative cholangiography was recommended by some to avoid bile duct injury[4,5]. In 1991 the present authors started evaluating laparoscopic ultrasonography as an alternative to intraoperative cholangiography. At the time there were no laparoscopic ultrasonographic probes available and an adapted probe was used for the first group of patients. At the same time a dedicated probe for laparoscopic ultrasonography was developed in collaboration with B&K Medical in Denmark. This new scanner was employed for the second group of patients. In the meantime other authors have demonstrated several advantages to the routine use of laparoscopic ultrasonography[11–14].

Both the sensitivity and specificity attained with laparoscopic ultrasonography in the authors' and other groups' experience[11–14] are similar to those reported for conventional intraoperative ultrasonography[6–8]. In this study laparoscopic ultrasonography visualized small bile duct calculi and sludge invisible on intraoperative cholangiography in five cases. Lane and Coupland[6] have already described this phenomenon with conventional intraoperative ultrasonography. These findings are even more significant because in both studies the ultrasonographic findings were known at the time intraoperative cholangiography was performed. In group 1 only a small number of unsuspected bile duct calculi was detected during operation. This small number explains the large difference in sensitivity between laparoscopic ultrasonography and intraoperative cholangiography. The overall accuracy rate of 98 per cent for both methods demonstrates their value more clearly.

In the second group both suspected and unsuspected common duct stones were treated laparoscopically, hence the significantly ($P = 0{\cdot}02$) higher number of common duct stones in the second group. Two of the four false-negative cholangiography findings in group 2 concerned patients in whom cholangiography had failed for technical reasons. One of these patients had Mirizzi syndrome. There were two false-positive findings for bile duct stones on laparoscopic ultrasonography in group 1. The first patient also had a positive cholangiographic examination. This was a patient in whom the stone could not be demonstrated by ERCP 2 days after operation. Bile duct calculi that cause acute pancreatitis are known to pass into the duodenum within 10 days in 84–95 per cent of cases[15,16]. In addition, the discrepancy between the number of bile duct stones found by routine intraoperative cholangiography and the incidence of sympatomatic stones left behind at cholecystectomy without cholangiography suggests that only one stone in 20 produces symptoms[17]. There is a possibility, therefore, that both the intraoperative modalities used did in fact show a true stone that had passed before ERCP was performed. The second patient was found to have a juxtapapillary diverticulum on intraoperative cholangiography, and the ultrasonographic findings were attributed to debris in this diverticulum rather than to a stone invisible on cholangiography. Laparoscopic ultrasonography with either of these scanners is at least as accurate as intraoperative cholangiography in finding bile duct calculi, and there is no difference between the adapted and dedicated scanners in this context.

In the beginning the reasons for routine performance of intraoperative cholangiography during laparoscopic cholecystectomy differed slightly from those in conventional cholecystectomy. More emphasis was placed on visualization of biliary anatomy, while the detection of common duct stones was considered of lesser importance[3,4]. The incidence of bile duct injury occurring during laparoscopic cholecystectomy may reach 1 per cent or more[18]. Routine intraoperative cholangiography is supposed both to diminish the number of bile duct injuries[5,19] and to increase the number of iatrogenic injuries detected immediately. While only the extrahepatic bile ducts can be scanned with the equipment used for laparoscopic ultrasonography in group 1, intraoperative cholangiography and the scanner used for group 2 are capable of showing the entire biliary tree. Intraoperative cholangiography had to be aborted for technical reasons in seven patients in group 1 and in ten in group 2, while laparoscopic ultrasonography was completed successfully in all patients. The Southern Surgeons Club, in fact, published a failure rate of 23 per cent for laparoscopic intraoperative cholangiography in 1991[20]. Laparoscopic ultrasonography has an additional advantage over intraoperative cholangiography in that it can be performed at any time during the operation, even before dissection has taken place. Laparoscopic ultrasonography detected variations of the biliary anatomy in 21 cases and intraoperative cholangiography in 20 cases in group 1. Twenty-two arterial anomalies were found by laparoscopic ultrasonography in the same group of patients. In group 2 the number of arterial variations ($n = 24$) was similar to that in the first group, whereas the number of biliary variations ($n = 50$) was significantly higher ($P = 0{\cdot}001$). A total of 65 patients were found to have a variation of either the arterial or biliary anatomy. This corresponds well with several anatomical studies on cadavers[21–23] that revealed anatomical variation in up to 65 per cent of cases These data indicate that in group 2 most anatomical variations present were demonstrated ultrasonographically. The only exception to this was the cystic artery, which is visible regularly only if colour flow Doppler scanning is used routinely. The distinction between the effect of the new probe and the increasing experience of the observer on the detection rate for anatomical variation is difficult to make. After the first 20 patients studied, the learning curve (*Fig. 1*) showed a constant rate of about five variations per ten patients in group 1. The rate in group 2 was similarly constant at about nine variations per ten patients. These findings suggest an improvement of the detection rate as a result of the new probe. The main difference between groups 1 and 2 with respect to the number of biliary variations at laparoscopic ultrasonography was found to be the number of dorsal cystohepatic junctions (seven *versus* 29 patients, $P = 0{\cdot}0001$) and the number of intrapancreatic junctions (six *versus* 17 patients, $P = 0{\cdot}0001$). As the two variations are often associated, this finding suggests that the dedicated ultrasonographic scanner permits better visualization of the pancreatic head.

Laparoscopic ultrasonography has the advantage of showing bile ducts and blood vessels, whereas intraoperative cholangiography demonstrates only the biliary tree. Cholangiography revealed a similar number of biliary anatomical variations to the number found with ultrasonography. The fact that the number of variations demonstrated by intraoperative cholangiography equalled those seen ultrasonographically can, at least to some extent, be explained by the surgeon's knowledge of the ultrasonographic findings at the time of performing intraoperative cholangiography. Another reason for the increase in anatomical variation found by cholangiography is the experience of the surgeons gained by routine application of the technique over 3 years.

Many surgeons refrain from using intraoperative cholangiography routinely because of the time necessary for the examination. The time taken for conventional intraoperative cholangiography is reported to be between 23 and 27 min[1,24] and the introduction of the laparoscopic technique has not reduced this[25,26]. In fact, the mean times of 16·4 and 13·5 min reported in the present study are the lowest published in a prospective trial so far. Both conventional intraoperative ultrasonography and laparoscopic ultrasonography with either scanner were significantly ($P = 0{\cdot}0001$) faster to perform[6,8,14], the mean time required was between 4 and 6 min

In conclusion, laparoscopic ultrasonography proved at least as accurate as intraoperative cholangiography in the detection of common duct stones. The detection of anatomical variations is improved by the dedicated scanner, although the surgeon's growing experience with the technique might have played a role as well. While considerable ultrasonographic experience was required for laparoscopic ultrasonography to be performed successfully with the adapted scanner, the specialized scanner capable of real-time imaging and colour flow Doppler scanning facilitates the use of laparoscopic ultrasonography for surgeons with little ultrasonographic experience. The new scanner also permitted better visualization of the pancreatic head and liver. The authors consider laparoscopic ultrasonography a reliable, quick and accurate alternative to intraoperative cholangiography during laparoscopic cholecystectomy.

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British Journal of Surgery 1996, **83**, 1517–1521

A Western surgical experience of peripheral cholangiocarcinoma

S. V. BERDAH, J. R. DELPERO*, S. GARCIA†, J. HARDWIGSEN* and Y. P. LE TREUT

*Department of Digestive Surgery and Liver Transplantation, La Conception Hospital, *Department of Oncologic Surgery, Paoli-Calmettes Cancer Institute and †Department of Pathology, North Hospital, Marseille, France*

Correspondence to: Professor Y P. Le Treut, Service de Chirurgie Digestive, Hôpital de La Conception, 147 Boulevard Baille, 13 385 Marseille Cedex 5, France

The aim of this retrospective study was to analyse outcome in 31 European patients operated on for peripheral cholangiocarcinoma between 1988 and 1995 (hilar cholangiocarcinoma was excluded). Before 1992, in addition to conventional resection, patients with irresectable tumour and with no extrahepatic metastasis underwent total hepatectomy with liver transplantation. Mild abdominal pain was the most frequent presenting clinical sign (11 of 31 patients) and jaundice was present in only four patients. Preoperative histological findings were available for 20 patients but the diagnosis was correct in only eight of these. Nineteen patients had curative surgery: 17 underwent conventional resection and two had total hepatectomy with liver transplantation. Major hepatectomy was performed in 12 of 17 cases, extended to the caudate lobe in five, to the bile duct confluence in four and to the retrohepatic vena cava in one. Postoperative mortality and morbidity rates were three and seven of 19 patients respectively, median survival was 15 months, and actuarial 1-, 2- and 5-year survival rates were 67, 40 and 32 per cent respectively. Twelve patients had only exploratory laparotomy because of the presence of extrahepatic metastasis or irresectable tumour. The invasive nature of peripheral cholangiocarcinoma can explain the limited number of resectable cases and the particularly unfavourable prognosis. Total hepatectomy does not provide survival benefit. Conventional surgery remains the only effective treatment, even for patients with advanced stage tumours.

Intrahepatic cholangiocarcinoma is the second most common primary liver cancer after hepatocellular carcinoma. However, it makes up only 10 per cent of primary liver malignancies, which explains the relatively low populations in the published series. The presence of specific aetiological factors such as hepatobiliary parasitosis or intrahepatic lithiasis makes these tumours more common in the Orient[1,2]. In Europe, their incidence is ten times lower[3].

Intrahepatic cholangiocarcinoma can be divided into two groups according to localization[4]: (1) peripheral cholangiocarcinoma which develops from small duct radicals within the liver; and (2) hilar cholangiocarcinoma, which develops from the major hepatic ducts near or at the junction of the right and left hepatic ducts. The two types differ in structure[5,6], symptoms and progressive neoplastic growth, and therefore require specific therapeutic approaches[7,8]. These differences are in part linked to tumour location relative to the major hepatic ducts: hilar tumours cause early obstructive jaundice, often providing an earlier diagnosis. However, the possibly more aggressive feature of peripheral cholangiocarcinoma could explain the higher incidence of intrahepatic and extrahepatic metastases at the time of diagnosis[9,10].

The aim of this retrospective study was to analyse 31 European patients operated on for peripheral cholangiocarcinoma.

Patients and methods

Between August 1988 and May 1995, 405 patients underwent laparotomy for liver tumour (321 malignancies). Some 339 resections were performed, 81 for benign lesions, 117 for primary and 141 for secondary liver cancers. During the same period, 147 total hepatectomies with liver transplantation were performed (23 for malignancy). In all, 177 operations for primary liver cancer were performed (117 resections, 43 exploratory laparotomies and 17 total hepatectomies with liver transplantation). There were 31 consecutive patients operated on for peripheral cholangiocarcinoma (18 per cent of the patients operated on for primary liver cancer): 23 men and eight women of mean age 56 (range 35–76) years. Ultrasonography and computed tomography (CT) were performed in all patients before operation. Angiography and/or magnetic resonance imaging was performed in eight patients before referral but was not used systematically as a preoperative diagnostic tool. Cavography was performed when invasion of the inferior vena cava was suspected. Twenty patients were referred with the histological or cytological results of a percutaneous biopsy of the tumour, but this procedure was not included systematically in preoperative investigations.

Laparotomy was indicated when the tumour was considered to be resectable No palliative resection was performed. In cases of resectable tumours, systematic lymphadenectomy of the porta hepatis was performed Until 1992, total hepatectomy with liver transplantation was carried out in patients with irresectable tumours and with no extrahepatic metastasis, following systematic exploratory laparotomy

Pathological examination was performed on operative liver specimens, or on large biopsies when resection was not possible. All specimens were re-examined for the purposes of the study. The diagnosis of cholangiocarcinoma was supported by gross and histological data. First, all patients had intrahepatic neoplasms; second, no extrahepatic abdominal primary site was detected during preoperative investigation or laparotomy; third, tumours exhibited the common histological features of cholangiocarcinomas. all were adenocarcinomas with small mucinous glandular structures and desmoplastic stromal response. Cases showing both mucinous and bile deposits were defined as combined hepatocholangiocarcinomas. Tumours were classified according to the criteria of the Union Internacional Contra la Cancrum[11].

No patient was lost to follow-up. Survival data were calculated from the date of resection or transplantation until 31 December, 1995 or the date of death. Actuarial patient survival was estimated by the Kaplan–Meier method. Operative mortality, defined as death within 30 days of surgery or during the same hospitalization, was not excluded from survival analysis.

Paper accepted 30 May 1996

Results

The mean time from the onset of symptoms to operation was 4·5 (range 1–19) months. The most frequent presenting clinical sign was mild abdominal pain ($n = 11$). Other signs at first presentation were palpable abdominal mass ($n = 4$), jaundice ($n = 4$), temperature ($n = 3$), pruritus ($n = 1$), weight loss ($n = 1$), phlebitis of the upper limb ($n = 1$) and Budd–Chiari syndrome with ascites. In five of the 31 patients, the tumour was found during a systematic ultrasonographic or biochemical check-up.

The morphological aspects of tumours on preoperative CT were: (1) solitary and infiltrating (18 patients) (*Fig. 1*); (2) multiple infiltrating (seven); (3) solitary and well defined (five); and (4) multiple and well defined (one). Hepatitis B virus serology was performed in 22 patients; three were positive for hepatitis B surface antigen. Of these 22 patients, six had hepatitis C virus serology; two were positive. The preoperative diagnoses were as follows: cholangiocarcinoma ($n = 14$). hepatocholangiocarcinoma ($n = 1$), hepatocellular carcinoma ($n = 6$), fibrolamellar carcinoma ($n = 3$), metastatic adenocarcinoma ($n = 5$) and malignant tumour ($n = 2$). Preoperative histological findings were available for 20 of the 31 patients. The diagnosis was correct in only eight cases.

The patients were divided into two groups (*Fig 2*) Nineteen patients (group 1) had resection with curative intent; two of these had total hepatectomy with liver transplantation. Twelve patients (group 2) did not undergo resection because of the presence of peritoneal dissemination (six cases), bilateral irresectable disease (five) and involvement of the confluence of the hepatic veins and retrohepatic vena cava (one). Four of these 12 patients underwent exploratory laparotomy before liver transplantation. Apart from these four patients and the two who underwent liver transplantation, 25 others were considered to have resectable tumours. However, resection was finally performed in only 17 of these.

Group 1: resection

The type of resection according to tumour stage is presented in *Table 1*. In the majority of cases, the surgical procedure was major hepatectomy: 12 of the 17 resections removed at least four segments. There were six extended right hepatectomies. The caudate lobe was removed on five occasions. Hepatic resection was extended to the biliary confluence and extrahepatic bile duct four times, to the diaphragm three times with one *en bloc* pulmonary wedge resection, and once each to the lesser curvature of stomach and the retrohepatic vena cava (which required a prosthetic replacement)[13] (*Fig. 3*).

The median duration of operation was 300 (range 180–600) min. The median number of blood units transfused during operation was 2 (range 0–13); only five patients received no transfusion. Median postoperative hospital stay was 28 (range 9–110) days.

Three of 19 patients died after operation, including one who had liver transplantation. The deaths were caused by respiratory failure (one patient), intra-abdominal bleeding (one) and small bowel perforation (one). Systematic lymphadenectomy was not responsible for any postoperative complication. Seven of the 19 patients developed non-fatal complications that required three reoperations. These included biliary fistula of the left

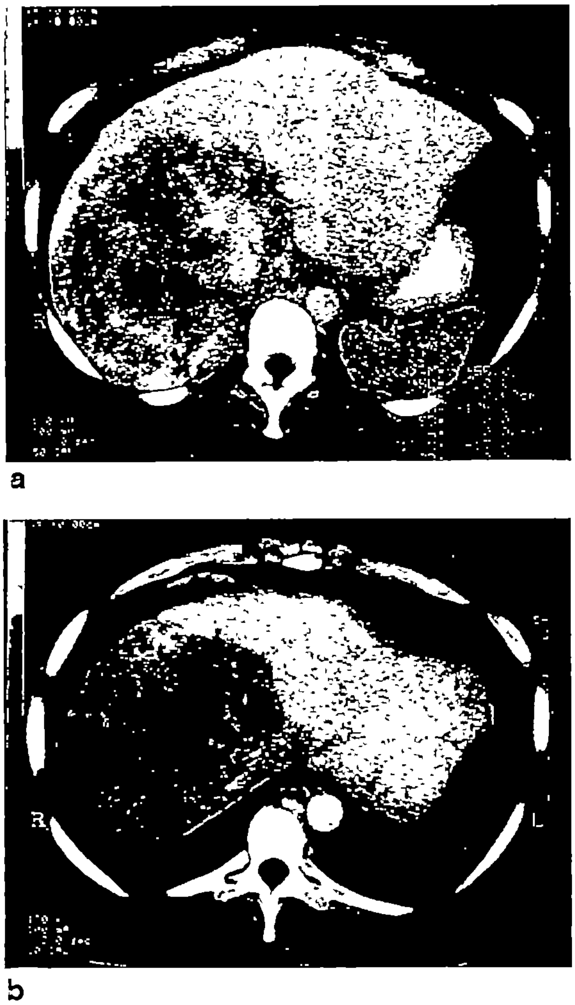


Fig. 1 Computed tomogram of a 15-cm tumour of the right lobe (patient no. 11). **a** Infiltrating and heterogeneous aspect. 1, 2 and 3 represent density measured by the radiologist **b** After injection of contrast medium, adjacent liver shows patchy enhancement suggesting Budd–Chiari syndrome Exploratory laparotomy found invasion of the confluence of the hepatic veins and the retrohepatic vena cava, and a nodule in the left lobe. The tumour was deemed irresectable and total hepatectomy with liver transplantation was performed

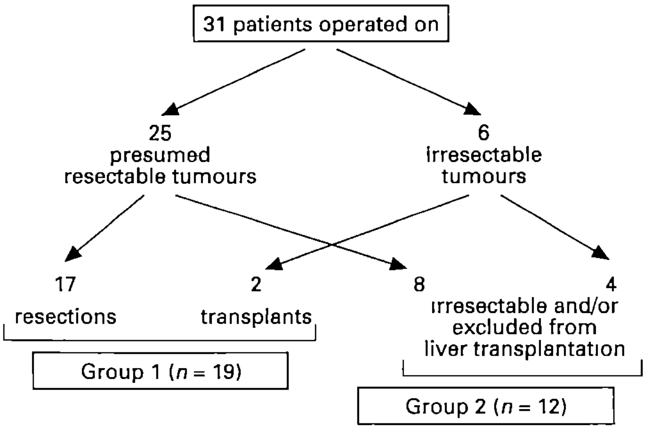


Fig. 2 Surgical management of 31 patients with peripheral cholangiocarcinoma

Table 1 Operation according to tumour stage in 19 patients with peripheral cholangiocarcinoma

Tumour size (cm)	Stage	Type of operation*	Survival (months)
13	IVa	Liver transplantation	16
15	IVa	Liver transplantation (*Fig 1*)	0 (postop. death)
14	IVa	Extended right hepatectomy and segment 1 resection, followed by transplantation for secondary biliary cirrhosis	90 (alive with disease)
8	III	Extended right hepatectomy and resection of bile duct confluence	74
8	II	Extended right hepatectomy and resection of bile duct confluence and diaphragm	30
10	II	Right hepatectomy	11
15	IVa	Extended right hepatectomy and resection of segment 1 and retrohepatic vena cava (*Fig 3*)	43 (alive with disease)
3	III	Extended right hepatectomy	4
14	III	Right hepatectomy and diaphragm and pulmonary wedge resection	8 (alive with disease)
5	II	Extended right hepatectomy	6 (alive with no evidence of disease)
18	III	Left hepatectomy and resection of segments 1 and 8	13
15	III	Left hepatectomy and resection of bile duct confluence	0 (postop. death)
7	II	Left hepatectomy and segment 8 resection	15
12	III	Left hepatectomy and segment 1 resection, and partial gastrectomy and resection of pericardium	8 (alive with no evidence of disease)
17	II	Left hepatectomy and resection of segments 1 and 8 and bile duct confluence	0 (postop. death)
5	II	Segmentectomy 5	6
5	III	Segmentectomy 4–5 and tumorectomy 8	62 (alive with disease)
8	III	Segmentectomy 4–5	18 (alive with no evidence of disease)
6	II	Segmentectomy 4–5	13

*According to Couinaud's nomenclature[12]

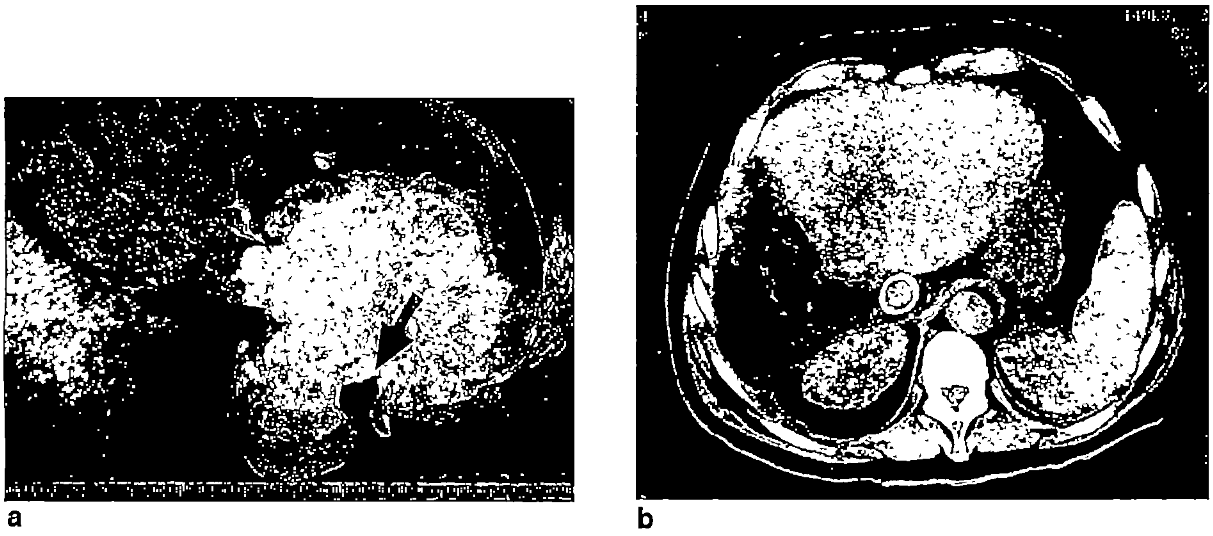


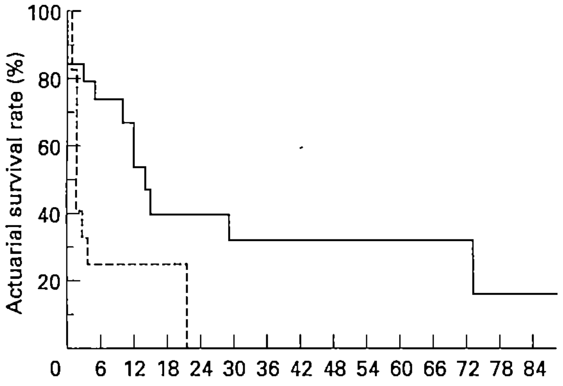
Fig. 3 Hepatectomy extended to the retrohepatic vena cava. a Horizontal slice of the resection specimen. The arrow shows stenosis of the retrohepatic vena cava. b Computed tomogram on day 20 after operation showing graft permeability

hepatic duct which required repair followed by total hepatectomy with liver transplantation 1 year after resection because of secondary biliary cirrhosis due to stenosis of the left hepatic duct. There was no evidence of local recurrence in the liver remnant. This patient is alive 90 months after the initial resection and has had a slow growing solitary lung metastasis for the past 3 years.

Overall median survival was 15 (range 0·1–90) months. The median survival of patients with stage II, III and IVa disease was 12, 14 and 16 months respectively. Overall actuarial 1-, 2-and 5-year survival rates were 67, 40 and 32 per cent respectively (*Fig. 4*). Seven patients are alive and three are free from disease.

Group 2: no resection

There was no postoperative death and no complications. Six patients underwent palliative systemic chemotherapy and one had chemoembolization. Median survival was 2 months. Two patients are alive 13 and 15 months after



No. at risk								
Resection	19	10	5	4	3	3	2	1
No resection	12	3	0	0	0	0	0	0

Fig. 4 Actuarial survival curve in patients who underwent curative resection (——, $n = 19$) and in non-resected patients (-----, $n = 12$)

operation and one died at 22 months. All other patients died before the fourth month.

Pathology

Ten patients (five in each group) had multiple lesions. The median size of resected tumours was 10 cm (the principal lesion was measured in patients with multiple lesions). There were 26 cholangiocarcinomas and five hepatocholangiocarcinomas. The adjacent liver was normal in 25 patients. There was fibrosis and fatty infiltration in three cases, cirrhosis in two and haemochromatosis in one. Lymph node metastasis was found in seven of the 19 resected patients.

Discussion

The present series is an analysis of the results of 31 patients operated on for strictly defined peripheral cholangiocarcinoma. The prognosis for peripheral cholangiocarcinoma differs from that of hilar cholangiocarcinoma. In recent series, most authors have analysed peripheral and hilar cholangiocarcinoma separately, despite the difficulties with positive diagnosis and differential diagnosis with hilar tumour or metastatic adenocarcinoma, even on resection specimens[14,15]. Preoperative biopsies are not reliable. Tumour morphology on preoperative imaging can orient the diagnosis[16,17]: metastases from adenocarcinoma are usually well limited ('pushing') and primary cancers are more infiltrating. In the present series most of the tumours (25 of 31) were infiltrating on preoperative CT.

The lack of aetiological factors differentiates the present and all Western series from Oriental series: 25 of the 31 patients had tumours that developed in normal liver parenchyma. On the other hand, the high rate of liverfluke infestation has made cholangiocarcinoma the leading cancer in north-east Thailand[3], and 16 of 20 resected peripheral cholangiocarcinomas were found to be associated with hepatolithiasis in a series from Taiwan[18]. Nevertheless, the prognosis is as unfavourable in the West as it is in the Orient, even after resection. In the present series, resected patients had a median survival of only 15 months, and actuarial 1- and 5-year survival rates were 67 and 32 per cent respectively. In addition, nine of the 12 non-resected patients died before the fourth postoperative month. The present results are comparable to those of series that analyse the results of surgical treatment for peripheral cholangiocarcinoma and exclude hilar cholangiocarcinoma (*Table 2*)[18–22].

The small number of patients in the published series cannot provide the data required for a study of prognostic factors. However, some influence of tumour stage on patient survival has been suggested[21,23]. Paradoxically, this correlation was not confirmed in the present series as the four patients surviving for longer than 36 months had stage III or IVa tumours. It would therefore seem that an advanced tumour stage does not preclude resection, when the tumour can be extirpated.

The early invasive character of peripheral cholangiocarcinoma can explain its unfavourable prognosis[9,17]. It can also explain the limited number of resectable cases[24]. In the present series, and despite extended resection, eight of the 25 tumours considered to be resectable before operation could not be resected, in large part due to the presence of bilateral disease or peritoneal dissemination. Laparoscopy with laparoscopic ultrasonography could avoid pointless laparotomy in such patients[25].

Attempts to improve prognosis or to treat irresectable tumours by total hepatectomy with liver transplantation have not lived up to expectations. There is recurrence in almost all cases and survival of more than 2 years is exceptional, even in patients with tumours discovered after transplantation for benign pathology[26,27]. Cholangiocarcinoma is therefore no longer considered as

Table 2 Results following curative surgery for peripheral cholangiocarcinoma

Reference	No. of patients	Median survival (months)	Actuarial survival (%)		
			1 year	3 years	5 years
Chen *et al.*[18]	20	21	70	56	—
Kawarada and Mizumoto[19]	11	—	64	34	34
Schlinkert *et al.*[20]	6	34	83	30	—
Pichlmayr *et al.*[21]					
Resection	32	13	80 (II)	40	30
			63 (III)	—	—
			52 (IVa)	—	—
Transplantation	18	5	14 (max. 25 months)		
Cherqui *et al.*[22]	15	14	58	32 (2 years)	—
Present series	19	15	67	32	32

an indication for liver transplantation by most authors[18,28]. The present authors have not used liver transplantation for peripheral cholangiocarcinoma since 1992, despite the long-term survival of 7·5 years in one patient who had a transplant for secondary biliary cirrhosis, 1 year after resection for cholangiocarcinoma.

Conventional surgery remains the only effective treatment for patients with these tumours. However, despite the progress in hepatic surgery that allows complete resection in an increasing number of patients, the prognosis is still poor. To date, non-surgical procedures have not appeared to provide survival benefit. Adjuvant chemotherapeutic protocols are the only hope for improving survival following surgery, or to allow inclusion of patients in liver transplantation programmes once again.

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British Journal of Surgery 1996, 83, 1522–1525

Surgery for biliary obstruction by tumour thrombus in primary liver cancer

B. TANTAWI, D. CHERQUI, J. TRAN VAN NHIEU*, M. KRACHT and P. L. FAGNIEZ

*Service de Chirurgie Digestive and *Département de Pathologie, Hôpital Henri Mondor, Université Paris-XII, Créteil, France*
Correspondence to: Dr D Cherqui, Service de Chirurgie Digestive, Hôpital Henri Mondor, 94 010 Créteil, France

Five patients with primary liver cancer presented with obstructive jaundice due to extension of tumour thrombus into the biliary ducts. Three patients had hepatocellular carcinoma, two of whom had alcoholic cirrhosis, and the other two had a peripheral cholangiocarcinoma. Preoperative diagnosis of biliary thrombus was best achieved by ultrasonography and computed tomography which showed peripheral hepatic tumour with dilated bile ducts containing dense material. All patients underwent liver resection associated with biliary exploration, clearance and T-tube drainage. Major hepatectomy was required in four cases. There were no postoperative deaths; one patient developed a subphrenic collection of bile which was drained percutaneously. All patients survived more than a year; median survival was 29 months. There are two long-term survivors without recurrence at 29 and 80 months. Patients with primary liver cancer and jaundice due to migrated tumour fragments in the common bile duct may benefit from surgical resection which can result in long-term resolution of symptoms and occasional cure.

Jaundice in patients with primary liver cancer usually occurs in later stages and results from diffuse tumour infiltration, hilar invasion or progressive liver failure. Prognosis in these cases is dismal, and death follows within a short time[1]. In a few cases, however, jaundice is caused by extension of tumour thrombus into the biliary ducts. Identification of this group of patients is important because surgical treatment may be beneficial.

The present paper reports experience with liver resection associated with bile duct clearance in five such patients.

Paper accepted 31 December 1995

Patients and methods

From January 1988 to January 1994, 166 patients underwent hepatic resection in this department Primary liver cancer accounted for 55 cases (33 per cent) including 12 patients with obstructive jaundice (22 per cent). Jaundice was due to extrahepatic hilar cholangiocarcinoma (Klatskin tumour) in four patients, central hepatic tumour invading the biliary confluence in three and extension of tumour thrombus into the biliary tree in five The latter five patients are the subject of this paper.

Location of liver tumours and type of liver resection were defined according to the segmental anatomy of Couinaud.

Details of the five patients are given in *Table 1*. Mean age was 60 (range 54–64) years. The primary liver cancer was hepatocellular carcinoma (HCC) in three patients and

Table 1 Clinical details of the five patients

Patient no.	Age	Sex	Diagnosis of biliary thrombus	Histology	Tumour size (cm)	Tumour location (segment)	Operative procedure	Outcome
1	64	F	Preoperative ERCP	HCC, cirrhosis	3	II–III	Bisegmentectomy II–III, bile duct clearance, T-tube drainage	Died at 33 months from recurrence
2	59	M	Preoperative ultrasonography and CT	HCC	4	VIII–IV	Extended right hepatectomy, bile duct clearance, T-tube drainage	Alive at 80 months without recurrence
3	63	M	CBD exploration during previous laparotomy	HCC, cirrhosis	9	IV–V	Extended right hepatectomy, bile duct clearance, T-tube drainage	Alive at 14 months with recurrence
4	54	F	CBD exploration during previous laparotomy	IHCC	8	II–III–IV	Left hepatectomy, bile duct clearance, T-tube drainage	Second liver resection for recurrence at 18 months; alive without recurrence 29 months after first surgery
5	59	M	Preoperative ultrasonography and CT	IHCC	15	IV–V–VIII	Extended right hepatectomy, bile duct clearance, T-tube drainage	Died at 22 months from recurrence

ERCP, endoscopic retrograde cholangiopancreatography, CT, computed tomography, CBD, common bile duct, HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma intrahepatic cholangiocarcinoma in two. Alcoholic cirrhosis was present in two patients with HCC.

Results

Clinical presentation

All patients had obstructive jaundice on admission with mean(s.d.) bilirubin level 129(91) (range 75–220) μmol/ml. Two patients had upper abdominal pain, but no patient had cholangitis.

Diagnosis was established at exploratory laparotomy for obstructive jaundice (in other centres) in two patients. Both had common bile duct exploration and plastic stent placement, and were referred secondarily. The other patients had no previous treatment and diagnosis was established by preoperative imaging. The most characteristic features were found on ultrasonography and computed tomography (CT), and included peripheral hepatic tumour with dilated bile ducts containing dense material. These features were found before operation in two patients treated entirely at this institution and at retrospective review of preoperative CT scan in the two patients who had previous laparotomy (*Fig. 1*). Two patients underwent endoscopic retrograde cholangiography (ERCP). In one it permitted preoperative diagnosis and in the other it showed persistent obstruction after stent placement (*Fig. 2*). Four patients underwent hepatic angiography before liver resection which showed hypervascular liver tumour without vascular extension.

The primary tumour was located in the left lobe in two patients, in the right lobe in two and in one patient it was central. Mean tumour size was 8 (range 3–15) cm.

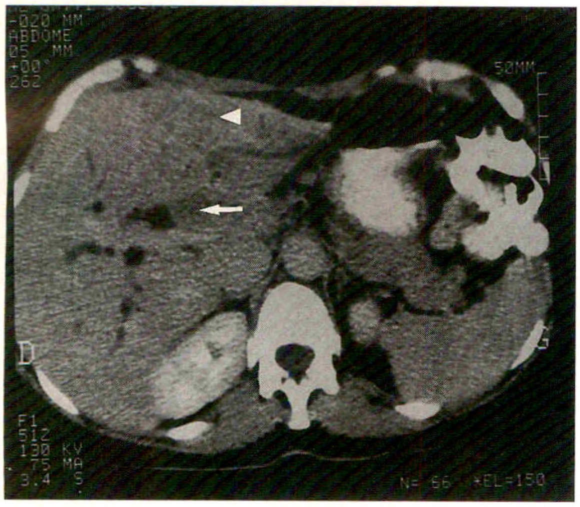

Fig. 1 Computed tomography scan from patient 4 (*Table 1*) showing infiltrative tumour of the left lobe of the liver (arrowhead) and dense material in the left biliary ducts corresponding to tumour debris extending down to the confluence (arrow). Biliary ducts of the right lobe are enlarged but do not contain dense material

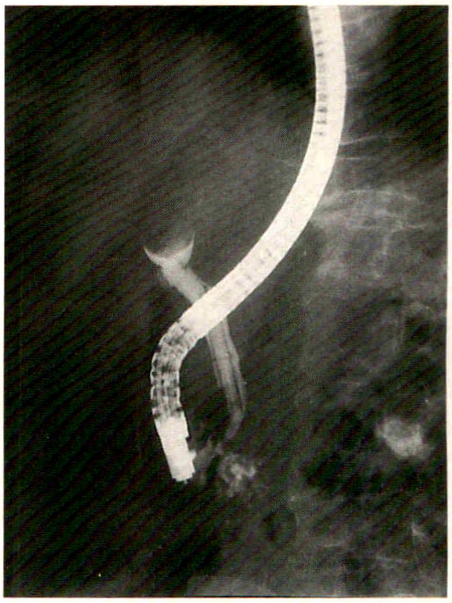

Fig. 2 Endoscopic retrograde cholangiogram showing obstruction of the upper part of the common bile duct by intraluminal tumour. A stent is visible in the lower part of the common bile duct. It was placed during first laparotomy performed before referral but was ineffective as it was located below the tumour

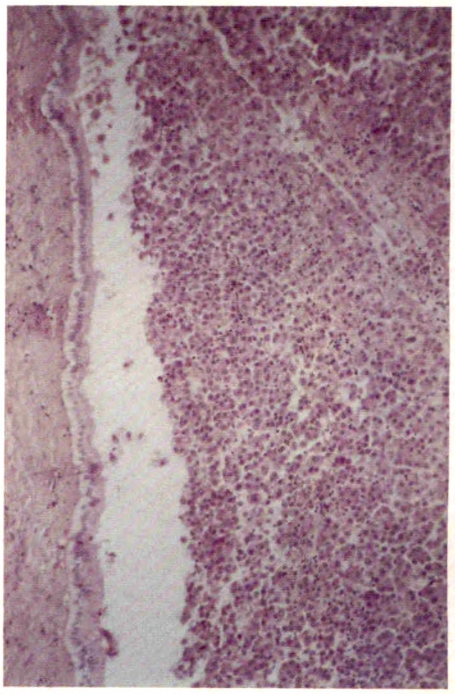

Fig. 3 Histology slide showing tumour thrombus inside a peripheral biliary duct. Normal bile duct epithelium is visible and is not invaded by the intraluminal proliferation of hepatocellular carcinoma. (Hematein–eosin–safran stain, original magnification ×120)

Operative procedures

Liver resection was performed in all patients including three extended right hepatectomies, one left hepatectomy, and one bisegmentectomy II–III. Bile duct exploration, clearance and T-tube placement was done in all cases. Three patients had a choledochotomy permitting extraction of tumour casts. The remaining two patients had the biliary tree cleared through the divided right or left hepatic duct after hepatectomy, followed by T-tube

Table 2 Liver resections reported for biliary extension of primary liver cancer

Reference	Year	Age	Sex	Tumour type	Treatment	Outcome
Caroli *et al.*[9]	1965	M	31	HCC	CD 2 RH	Alive without recurrence at 3 months
Capelle *et al.*[10]	1972	M	63	HCC	RH	Died 2 days after surgery
Ohmori *et al.*[11]	1975	NA	NA	HCC	RH	Alive without recurrence at 10 months
Afroudakis *et al.*[12]	1978	F	15	FLC	ELH	Alive without recurrence at 22 months
Tzuzuki *et al.*[8]	1979	M	51	HCC	ERH	Alive without recurrence at 24 months
VanSonnenberg and Ferrucci[13]	1979	F	51	IHCC	LH	Recurrence at 6 months
Kojiro *et al.*[14]	1982	NA	NA	HCC	LH	Alive without recurrence at 10 months
Lee *et al.*[15]	1984	NA	NA	HCC	LH + CBD resection	NA
		NA	NA	HCC	ERH + CBD resection	NA
Albaugh *et al.*[16]	1984	F	24	FLC	LH + ERCP	Recurrence at 6 months; alive after more than 24 months
Lau *et al.*[17]	1990	M	57	HCC	LH	Recurrence at 17 months; alive
		M	71	HCC	1 ERCP 2 RH	without recurrence at 24 months
Roslyn *et al.*[5]	1984	M	65	CH	LH	Died at 40 months
Capizzi *et al.*[18]	1992	M	70	IHCC (mucinous)	LH	Alive without recurrence at 60 months

HCC, hepatocellular carcinoma; FLC, fibrolamellar carcinoma; IHCC, intrahepatic cholangiocarcinoma; CH, cavernous haemangioma; CD, choledochoduodenostomy; RH, right hepatectomy; LH, left hepatectomy; ELH, extended left hepatectomy; ERH, extended right hepatectomy; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct; NA, not available

insertion through the severed duct. Clearance of the biliary tract was easily achieved in all cases since tumour thrombi were not adherent to the bile duct wall.

Pathology

In all patients, biliary obstruction was due to tumour thrombus originating from the primary tumour and growing continuously along the biliary tract lumen resulting in tumour casts. Tumour thrombi were not adherent to the bile duct wall and did not invade it; they resulted from rupture of the primary tumour in the peripheral biliary tract (*Fig. 3*). Jaundice occurred when tumour thrombus occluded the biliary confluence and common bile duct and was not due to direct invasion of the hepatic hilum. Histologically, the obstructing thrombi consisted of vascularized but partially necrotic primary tumour tissue.

Outcome

There was no postoperative death. One patient had prolonged postoperative jaundice and an intra-abdominal bile collection which was drained percutaneously. The postoperative course was uneventful in the remaining four patients.

All patients survived more than a year; median survival was 29 months. One patient is alive without recurrence 80 months after surgery. The four other patients developed intrahepatic recurrence. One patient had localized recurrence without biliary obstruction at 18 months and had a second liver resection; she is alive and free from disease 29 months after first resection. In another patient, recurrence was treated by percutaneous ethanol injection and hepatic arterial chemoembolization; he is alive 14 months after surgery. Two patients had tumour recurrence with jaundice due to biliary obstruction. One died at 33 months without treatment. The other underwent percutaneous stenting and died at 22 months.

Discussion

Patients with primary liver cancer occasionally develop tumour rupture into the adjacent biliary tract. In these patients, obstructive jaundice may occur by one of three mechanisms: haemobilia, migration of tumour debris which separates from the primary growth or continuous retrograde growth along the biliary tree[2-8]. The latter mechanism applied in these five patients, and jaundice occurred when tumour thrombus occluded the biliary confluence and common bile duct.

Intraluminal biliary obstruction is a rare complication of primary liver cancer; a literature search identified 127 cases[2-29]. HCC is the most frequently involved tumour (94 of 127 cases, 74 per cent). The other types of tumour are cholangiocarcinoma (6 per cent and two cases in this series), mixed tumours and sarcomas. It has also been reported with secondary liver cancers[30,31]. This complication is an illustration of the tendency of liver tumours to invade adjacent luminal structures and grow inside them. In the case of HCC it is the equivalent of portal or hepatic venous extension which is, however, more common. Biliary extension was not associated with vascular extension in patients from this study.

This complication must be differentiated from jaundice due to hilar invasion, diffuse tumour infiltration or progressive liver failure for which there is no chance of cure. Preoperative diagnosis of biliary thrombus was best achieved in this group by ultrasonography and CT which showed a peripheral hepatic tumour with homolateral dilated bile ducts containing dense material corresponding to tumour debris. Contralateral bile ducts were dilated but did not contain dense material (retained bile) (*Fig. 1*). ERCP is not required in most cases because it shows only distal obstruction and therefore is less specific than ultrasonography and CT, and it carries a risk of cholangitis. Angiography is indicated for technical purposes or when vascular extension is suspected.

The present results suggest a benefit from aggressive surgical management in patients with biliary tumour thrombus. The goals of operation in these patients are biliary decompression with removal of tumour debris or blood clots and resection of the hepatic tumour. Radical hepatic resection with bile duct clearance is the ideal procedure and was achieved in all the patients. All survived more than a year with excellent palliation and two patients are alive without recurrence at 29 and 80 months.

Of 127 cases reported in the literature, 63 patients (50 per cent) had surgical treatment, but curative hepatic resection was performed in only 14 of these (22 per cent)[6,8–18]. Details of these 14 patients are listed in *Table 2*. Outcome was available in 12 of these patients of which at least seven were alive more than 1 year after surgery. The other patients had palliative treatment with biliary decompression by various techniques including removal of tumour debris with T-tube insertion, biliary enteric bypass or internal biliary stenting[3,6,10,12,13,19]. In an unspecified number of patients decompression of the obstructed biliary tract was achieved endoscopically. The tumour fragments were extracted and a nasobiliary drain or an endoprosthesis inserted[3,12,13,15].

Migration of tumour fragments in the biliary tract can be recognized by careful analysis of imaging in some patients with liver tumours and jaundice. This diagnosis may be useful as surgical resection is often possible in these patients and may result in long-term resolution of symptoms and occasional cure.

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British Journal of Surgery 1996, 83, 1526–1529

One hundred and fifty hepatic resections: evolution of technique towards bloodless surgery

M. REES, G. PLANT, J. WELLS and S. BYGRAVE*

*Hepatobiliary Unit, North Hampshire Hospital, Basingstoke, and *Wessex Cancer Intelligence Unit, Winchester, UK*
Correspondence to: Mr M. Rees, Hepatobiliary Unit, North Hampshire Hospital, Basingstoke RG24 9NA, UK

A technique of hepatic resection is described and the results of 150 resections are reviewed. Hepatic transection was performed, under intermittent portal inflow occlusion, using ultrasonic aspiration to skeletonize portal branches and venous tributaries. Control of venous haemorrhage during resection was optimized by argon beam coagulation and lowering central venous pressure to between 0 and 4 cmH_2O by extradural blockade and systemic nitroglycerine infusion. One patient with jaundice died in hospital, giving a mortality rate of 0·7 per cent. There were no deaths in patients without jaundice and cirrhosis. Fifteen patients (10.0 per cent) had significant complications, nine medical and six surgical, including three bile leaks (2.0 per cent). Mean blood loss was 814 ml for the whole study but only 434 ml in the last 4 years. During this latter period mean blood transfusion in hospital was 0·5 units and mean postoperative haemoglobin value fell by 0·7 g per 100 ml. Hepatic resection can be performed with the same degree of confidence and similar low morbidity as any other major surgical procedure.

This century has seen a gradual evolution of surgical technique throughout the world, as hepatobiliary surgeons have striven towards safe and bloodless liver surgery. Two seminal discoveries have driven this evolution. Morbidity and mortality from liver resection is closely correlated to major blood loss at the time of surgery[1–4]. Moreover, there is evidence that increased blood transfusion during hepatic resection for malignancy is associated with diminished long-term survival[5–7].

In this paper experience of 150 liver resections between 1986 and 1995 is reported, and the technique that has evolved to encapsulate recent advances is described.

Patients and methods

Surgical technique

The patient is anaesthetized and standard arterial and venous lines are inserted. A catheter is placed to administer a thoracic or high lumbar extradural block. An infusion of nitroglycerine (Lipha Pharmaceuticals, West Drayton, UK) is started at 1 mg/h (50 mg in 50 ml saline) and titrated to achieve optimal lowering of central venous pressure (CVP) without deleterious arterial hypotension. The usual dosage is 3 mg/h but can be much higher. A CVP of 0–4 cmH_2O is usually achieved without significant systemic hypotension. A dopamine infusion at low dose (3 mcg/kg/min) is run throughout the procedure and into the early postoperative period. Intravenous aprotinin 10^6 units (Bayer, Newbury, UK) is given before division of the liver[8]. Any clotting deficiencies are corrected both before operation and during surgery by infusion of fresh frozen plasma as required.

The patient is placed supine with the right arm elevated and secured across the table. An exploratory right subcostal incision allows assessment of resectability by palpation of the liver and confirmation of the absence of peritoneal disease or fixed porta hepatis nodes. The incision is then extended from the midline to the tip of the 12th rib and superiorly to the xiphisternum. An extension to the left of the midline is added in patients with a narrow costal margin. The liver is mobilized by division of the falciform ligament to expose the superior vena cava followed by division of the left and right triangular ligaments. Resectability is reconfirmed by bimanual palpation and intraoperative ultrasonography, and the resection margins are outlined by diathermy. Where tumour extends to the intersegmental borders, a 1- or 2-cm margin is taken in a perisegmental fashion as described by Scheele[9].

Large tumours adherent to the dome of the diaphragm are mobilized by *en bloc* resection of involved diaphragm. Bleeding from the diaphragm edge is controlled and, depending on the size of defect, the diaphragm is closed either primarily with no. 1 polyglactin or by polypropylene mesh. Tumours that are adherent posteriorly can usually be mobilized in a plane deep to the peritoneum and superficial muscle layer of the diaphragm but preserving the diaphragm intact.

In right hepatectomy, the retrohepatic vena cava is exposed by dividing small veins from the right caudate process. More superiorly, the hepatocaval ligament is divided to expose the right hepatic vein[10]. The right hepatic vein may be divided as a preliminary or at the end of the transection. Where possible, it is divided early between two vascular clamps and under-run with two layers of 3/0 polypropylene. Care must be taken not to narrow the vena cava at this point, which could create an area of high pressure and a Budd–Chiari syndrome. If the vein is not easily exposed or if the surgeon is relatively inexperienced the right hepatic vein is probably best left at this stage and secured from within the liver during transection. When performing left hepatectomy the same principles apply.

The porta hepatis is dealt with next. In right hepatectomy the portal structures are divided in the following order. After standard cholecystectomy, the right hepatic artery is dissected and divided as close as possible to the hilum and suture ligated. Before division, a left hepatic arterial pulse is confirmed. The portal vein is then mobilized after division of the right caudate branch as a preliminary to avoid injury. The right portal vein is tied close to this junction with a 3/0 polyglactin tie which allows division between two clips and suture ligation. The right hepatic duct may be divided at this stage but usually will be taken after hepatic transection and divided at least 1 cm away from the right/left duct junction. If difficulty is encountered with extrahepatic dissection of the porta hepatis, the right portal structures may be dissected outside the Glissonian capsule or after transection of the liver which can open up the porta like the leaf of a book.

Before left hepatectomy dissection follows a similar pattern, but if the caudate lobe is to be preserved care is taken to divide the portal structures above the left caudal branches.

Paper accepted 8 December 1995

In classical resections of right and left hepatectomy, lateral segmentectomy of II and III and extended right and left hepatectomy, division of the portal inflow allows demarcation of the transection plane. For segmental resection the plane of surgery is determined by palpation and intraoperative ultrasonography, based on sound anatomical knowledge[11,12].

When performing right or left hepatectomy, large packs are placed behind the right lobe to lift it superiorly and to the left so that during transection the plane of the main fissure is near vertical. This allows easier orientation and also reduces hepatic venous pressure during transection. The hepatoduodenal ligament is mobilized and a soft bowel clamp is applied (Pringle manoeuvre)[13]. The clamp is kept on for 20 min and released for 3–4 min. During difficult manoeuvres the clamp has been left on for 1 h without any serious mishaps[14–16].

The liver capsule is divided using coagulation diathermy and the liver is transected using an ultrasonic aspirator (CUSA, Valley Lab, London, UK or Selector, Surgical Technology Group, Andover, UK)[17]. During transection, 70 per cent power is applied unless the liver is fibrotic when power may need to be increased to 90 per cent. Key points that optimize the use of an ultrasonic aspirator are as follows: the operating hand should be kept supple with gentle forward movements; because the power is directed forwards, side to side waving of the handpiece is unproductive; and as the susceptible liver parenchymal cells are destroyed, the portal structures are easily displayed. The capsular extension that surrounds portal divisions makes them particularly resistant to ultrasonic damage. In contrast, hepatic vein tributaries are easily penetrated and extra care is taken when dissecting the larger hepatic veins. For a beginner, this is best achieved by reducing the power of the aspirator. During transection, blood loss should be minimal as portal branches and venous tributaries are skeletonized. Small branches of less than 1 mm are coagulated using the argon beam coagulator (Surgical Technology Group). Larger branches are secured by a 3/0 polyglactin ligature on the preserved side and a metal clip on the specimen side (Ligaclip; AutoSuture, Ascot, UK). Larger veins such as branches of the middle hepatic vein are secured by 3/0 polyglactin suture. During transection, any small holes that are made in the larger venous or portal branches of the vein can be sealed temporarily using the argon beam coagulator to allow the surgical aspirator to identify the structure more clearly. Towards the end of the transection extra care is taken to identify the appropriate hepatic veins which are then double clamped with vascular clamps and under-run with 3/0 polypropylene.

After removal of the specimen, the transected surface is observed carefully and small bleeding points are secured with argon beam coagulation. If there are any persistent sites of oozing, they are under-run with 6/0 polypropylene. A careful search is made for any bile leaks, by gently dabbing the surface with a white swab. Finally, the surface is covered with collagen sheets (Johnson and Johnson Medical, Ascot, UK) or sprayed with coagulant glue (Tisseel Immuno, Sevenoaks, UK) if there is a problem with haemostasis. The wound is closed in layers with one tube drain in the subdiaphragmatic space. On three occasions, when the vena cava was involved, transection was performed under total vascular occlusion as described previously by others[18–21].

After operation the patients are observed in the high dependency unit for 1 night and returned to the ward thereafter. All patients have epidural analgesia which is maintained for 4 days.

Patients

Between 1986 and 1995, 150 hepatic resections on 143 patients were performed by one surgeon at the North Hampshire Hospital. Mean age was 58 (range 18–86) years; 82 resections (55 per cent) were carried out in men. The indication for resection in 114 patients (76 per cent) was metastatic colorectal cancer (*Table 1*). Two-thirds of operations were standard right or left hepatectomy (*Table 2*), although 28 included concurrent wedge or segmental excision of the other lobe. Extended right hepatectomy implied complete excision of segment IV in continuity with segments V–VIII. Extension of a right hepatectomy to include only partial excision of segment IV (IVa or IVb) was grouped under right hepatectomy. Atypical resections were performed in seven reresections where normal anatomical planes were distorted and in one case to minimize parenchymal loss in an elderly patient.

Table 1 Indication for hepatic resection in 150 patients

Colorectal metastases	114
Sarcoma metastases	9
Carcinoid metastases	4
Primary liver tumour	5
Benign tumour	7
Metastases of malignant schwannoma	2
Metastases of gastric carcinoma	1
Metastases of oesophageal carcinoma	1
Klatskin tumour	1
Metastases of melanoma	1
Direct invasion of gallbladder carcinoma	1
Direct invasion of hypernephroma	1
Liposarcoma recurrence	1
Metastases of squamous cell carcinoma of the anus	1
Metastases of uterine carcinoma	1

Table 2 Surgical procedures performed during 150 resections of the liver

Right hepatectomy*	77
Left hepatectomy†	23
Extended right hepatectomy	7
Extended left hepatectomy	1
Lateral segmentectomy (II and III)	7
Segment oriented resection	27
Atypical and multiple wedge excisions‡	8

*Additional left-side procedures were required in 21 cases; †additional right-side procedures were carried out in seven; ‡seven repeat resections

Results

One patient died in hospital or within 30 days, giving a mortality rate of 0·7 per cent. This patient, who had jaundice (bilirubin level above 600 mg/dl), underwent extended right hepatectomy with resection of the vena cava and Roux loop biliary reconstruction. There were no deaths in patients without jaundice and cirrhosis. Of the 149 patients who left hospital, one died within 3 months and two more within 6 months (both from carcinomatosis 5 months after resection of non-colorectal tumours). The total mortality rate within 6 months was 2·7 per cent.

Thirty-five patients (23·3 per cent) had a postoperative complication of which 29 were general and six specific surgical complications. Of the general complications, 20 were minor including chest infection (seven), pneumothorax (one), urinary tract infection (three), urinary retention (two), partial small bowel obstruction (three) (all treated conservatively), one cardiac arrhythmia, one possible pulmonary embolism, one sacral ulcer (in a paraplegic patient) and one mild hepatic insufficiency. Five patients had more serious and prolonged problems including pneumonia (one), hepatic insufficiency (two), cholangitis (one) and paralytic ileus (one). Four patients had life-threatening events which required intensive care. These were pulmonary embolism, severe pneumonia, cardiac arrhythmia and hepatic failure.

All resolved with conservative management. There was no evidence of postoperative renal failure.

Six patients had surgical complications. Three patients had a bile fistula; two resolved spontaneously and one required percutaneous drainage and endoscopic stenting. Three patients had life-threatening surgical problems. One secondary haemorrhage on the eighth day from a jejunal Roux loop anastomosis required under-running of a small vessel. Two patients had hepatic insufficiency 4 and 6 weeks after extended right hepatectomy. Both developed bile duct obstruction. One had kinking of the left hepatic to common hepatic duct junction, treated by percutaneous biliary stenting. One developed an ischaemic stricture of the left duct which required Roux loop diversion.

Mean postoperative hospital stay was 12 (range 6–73) days. Mean blood loss for all patients was 814 (range 70–10 000) ml with a mean blood transfusion requirement during the whole hospital stay of 1·9 units. Mean fall in blood haemoglobin concentration in all patients was 0·4 g per 100 ml. The first 30 cases were arbitrarily analysed separately to illustrate the learning curve in liver resection. Mean blood loss was 2613 (range 100–10 000) ml, mean blood transfusion requirement 5·8 units and mean fall in haemoglobin level 0·2 g per 100 ml. The argon beam coagulator was introduced in 1991; 83 patients have undergone resection with ultrasonic dissection and argon beam coagulation. Mean blood loss in these patients was 434 (range 75–1700) ml and mean blood transfusion requirement in hospital 0·5 (range 0–5) units. Sixty patients (72 per cent) did not require transfusion. Mean fall in haemoglobin level during the hospital stay was 0·7 (range −6 to +4·8) g per 100 ml. Concealed blood loss was calculated on the assumption that 1 unit blood (450 ml) contains 1 g haemoglobin. The concealed blood loss after operation before the argon beam coagulator was introduced was zero; after the coagulator was introduced it was 90 ml. No patient required reoperation for bleeding from the liver.

Discussion

The technique of liver resection has evolved such that many centres throughout the world are reporting major liver surgery with minimal blood loss and minimal morbidity and mortality rates[1,19–25]. The authors have evolved a technique that compares favourably with these results. It was found that blood loss has reduced over the years so that transfusion is rarely required. We believe that in this series we were overgenerous in blood replacement in earlier patients, as a consequence of an initial belief that liver surgery would always incur extreme blood loss. Other workers have proposed withholding blood transfusion until the haemoglobin level has reached 8 g/dl or less[26–28]. This approach is new to British surgical practice and deserves further evaluation. In the present study, the possibility of concealed haemorrhage after operation was excluded by the absence of any fall in postoperative haemoglobin level. These results confirm that reactionary haemorrhage on the transected surface is not significant with the technique described.

The most significant factor in achieving bloodless liver surgery is the experience of the surgeon. Other factors include adequate exposure, which can usually be gained through a subcostal incision with strong mechanical retraction, to allow gentle mobilization of the liver. Meticulous haemostasis of wound edges and the divided diaphragm is mandatory. Division of portal structures and hepatic veins is best achieved by well described vascular techniques, with suture ligation of all large vessels before removal of the vascular clamp.

The anaesthetist's role includes insertion of an epidural catheter which, in addition to providing postoperative analgesia, facilitates lowering of CVP. CVP is further lowered to between 0 and 4 cmH_2O by fluid restriction (often to the point of oliguria) and nitroglycerine infusion. The dominant effect of nitroglycerine is venodilatation which reduces preload and CVP with a smaller effect on arterial pressure. During the first 3 years of this experience, CVP tended to be higher, between 6 and 10 cmH_2O. This made control of hepatic venous tributaries more difficult and thereby increased blood loss. At the lowered level of CVP the potential for air embolism has not been a problem. If small air emboli have occurred these have not been detectable. One patient, not included in this series, did develop a probable air embolus where there was a sudden cessation of end-tidal carbon dioxide excretion and a rapid rise in CVP, followed by cyanosis and systemic hypotension. This lasted 20 min, following which the patient made an uneventful recovery. Despite fluid restriction, renal failure has not occurred in any patient in this series. Although all patients have short periods of oliguria during the procedure, the urine output has always rapidly returned to normal when fluid is given after removal of the specimen.

Blood spillage during transection of the liver is reduced using inflow occlusion. The liver will tolerate more than 2 h of normothermic occlusion without major complications[14–16] but the authors' practice is to remove the 'Pringle clamp' every 20 min for 3–4 min following an uncontrolled observation that this appears to be associated with less metabolic acidosis. Extension of the concept of vascular occlusion by Heaney *et al.*[18] to isolate the liver totally by the addition of vena caval clamps and even aortic clamping is rarely needed. However, involvement of the vena cava in three patients necessitated this manoeuvre and the principles of the technique should be familiar to any liver surgeon[18–21].

The ultrasonic aspirator[17] allows gentle and precise resection of the liver parenchyma with clear skeletonization of the portal structures and hepatic veins. This is a clear advance over techniques employed previously such as finger fracture or blunt dissection[29,30] and the method is now widely accepted. Other techniques such as water jet dissection also have their proponents[31].

The addition of argon beam coagulation enhances the effectiveness of ultrasonic aspiration in reducing blood loss[32,33]. It is particularly useful for sealing small holes in hepatic venous tributaries, while the vessel is skeletonized. This cannot be done by ordinary diathermy because the depth of coagulation enlarges the hole and precipitates further bleeding. Larger holes require careful suturing. The authors' rule is to stop all bleeding before proceeding.

In conclusion, major blood loss in liver surgery should be exceptional. Good operative technique is imperative and mechanical aids for transection are vital. The overall blood loss, as measured in this series, together with the minimal morbidity and mortality rates, should encourage clinicians to look at liver resection in the same light as other operative procedures. The authors would agree with Huguet[28] that 'the aim at the end of this century is the performance of all types of hepatic surgery without blood loss'.

Acknowledgements

The authors thank Marilyn Clegg, Research Assistant, and the Wessex Cancer Trust, Basingstoke Surgical Cancer Project and Wessex Cancer Intelligence Unit for their continued support. Particular thanks are due to Professor Johannes Scheele, Jana, Germany, for inspiration, advice and support.

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British Journal of Surgery 1996, 83, 1530–1531

Successful use of size-mismatched liver allografts in children by delayed primary closure of the abdominal wall

A. S. SOIN, P. J. FRIEND, G. NOBLE-JAMIESON*, C. J. E. WATSON, N. V. JAMIESON, R. Y. CALNE and N. BARNES*

*University of Cambridge Clinical School, Departments of Surgery and *Paediatrics, Addenbrooke's Hospital, Cambridge, UK*
Correspondence to: Mr A. S. Soin, Department of Surgery, Level 9, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK

Children who are too ill to await a liver graft of suitable size may be transplanted with a relatively oversized graft by leaving the abdominal wound partially open, the defect being bridged with polypropylene mesh and the mesh reduced in stages until it can be removed and the wound directly closed. This technique has been used in seven children who received nine grafts (five reduced and four full size). Their mean age was 7·3 (range 0·5–11) months and mean weight 5·8 (range 2·3–7·2) kg. Progressive reduction in the size of the transplanted liver made primary closure possible in survivors in up to four stages. Over a follow-up period of 3 to 58 months, five of the nine grafts and five of the seven patients survived. No significant complications attributable to the technique were encountered. The technique of delayed primary abdominal wall closure may be of benefit in children at risk of graft failure because of a size-mismatched graft.

The scarcity of donor livers of appropriate size is the most important constraint on paediatric liver transplantation. Although the use of reduced-size grafts has increased the potential donor pool, there is still an appreciable waiting-list morbidity and mortality, especially in very small children[1]. Larger than ideal grafts may therefore have to be accepted for very sick and small children. In such cases, the authors have adopted the policy of using a mesh to achieve temporary cover of the abdominal wound without tension and allow delayed primary closure of the abdominal wall, to avoid compression of the oversized graft and thus reduce the risk of graft infarction. Experience with this technique is presented here.

Patients and methods

Technique of delayed primary closure

The reduced- or full-size liver graft was implanted as previously described[2]. The incision was closed only so far as was possible without undue compression of the abdominal contents. The rest of the incision was left open and the edges of the muscle layer were sutured to a sheet of polypropylene mesh which was cut to the size of the defect. The skin edges were not apposed and the mesh was covered with a sterile occlusive dressing.

The degree of abdominal tension was assessed daily and the mesh size was reduced in stages over 1–7 weeks. This was done in the operating theatre under general anaesthesia by either excising the central portion of the mesh and suturing the edges together or trimming one side and resuturing it to the muscle layer. When the abdomen was soft enough to be closed completely, the mesh was excised and the incision closed in layers.

Recipients and donors

This technique has been used in seven children (five girls and two boys) receiving nine grafts. Their mean age was 7·3 (range 0·5–11) months and mean weight 5·8 (range 2·3–7·2) kg. The mean donor age was 7·3 (range 2–31) years and weight 21·1 (range 11–50) kg. Five grafts were reduced and four were full size. The details of the donors and recipients are shown in *Table 1*. The follow-up period ranged from 3 to 58 months.

Postoperative management

Fluid, electrolyte and protein losses across the mesh were not significant problems with the use of occlusive wound dressings. All but one of the surviving patients were fed enterally after the immediate postoperative period. Patient number 4 required prolonged parenteral nutrition (8 weeks). The patients were weaned from ventilation according to the usual indications and transferred to the general ward from the intensive care unit (*Table 1*) after 1–4 days of extubation.

Results

Delayed primary closure

This was achieved in all patients with surviving grafts in one to four stages after 1–7 weeks.

Complications

There were no complications that could be attributed to the technique. Multiple intestinal perforations requiring 11 additional laparotomies occurred in patient number 4, but none of the perforations was in the bowel loops in contact with the mesh. In the past, the authors and others[3] have encountered unexplained multiple intestinal perforations in small recipients of liver grafts in the postoperative period even with immediate primary abdominal closure. The authors therefore believe that this complication was unrelated to the method of closure. In patient number 2 *Staphylococcus aureus* was grown from a wound swab on day 7. This infection resolved after 10 days of treatment with oral flucloxacillin. There was no obvious purulent discharge, the mesh was retained and the operative plan was not altered. Therefore, apart from the gut perforations, no serious abdominal infective complications were seen. The wounds have healed well and no incisional hernias have occurred in the five survivors.

Paper accepted 12 January 1996

Table 1 Characteristics of patients and grafts where delayed primary closure was used

Patient no.	Graft no.	Recipient age (months)	Recipient weight (kg)	Donor age (years)	Donor weight (kg)	Graft type	No. of stages	ICU Time in (days)	Time to closure (weeks)	Follow-up (months)	Fate of graft
1	1	0·5	2·3	3	14	LLS	—	—	—	—	Infarction*
2	2	6	7·2	3	15	W	2	4	3	58	Normal
3	3	11	5·5	2	12	W	3	30	1	29	Normal
4	4	8	6·5	10	31	RTS	4	67	7	14	Normal
5	5	8	6·5	2·5	11	W	1	8	2	13	Normal
6	6	7	6·5	6	18	LLS	—	—	—	—	HVT†
6	7	7	7·0	3	11	W	—	—	—	—	PNF‡
6	8	7	7·0	5	28	LLS	—	—	—	—	CVA§
7	9	11	6·5	31	50	LLS	3	31	7	3	Normal

*Patient died from graft infarction secondary to portal vein and hepatic artery thromboses on day 3. †Graft failed on day 1. ‡Graft failed on day 2. §Patient died from haemorrhagic cerebrovascular accident (CVA) with a viable graft. LLS, left lateral segment; W, whole graft; RTS, right trisegmental graft (with left lateral segment resected); ICU, intensive care unit; HVT, hepatic vein thrombosis; PNF, primary non-function

Survival

Five of the nine grafts and five of the seven patients have survived with normal graft function.

Causes of graft failure

Three grafts failed: one due to hepatic vein thrombosis on day 1, one due to primary non-function on day 2, and one due to portal vein and hepatic artery thromboses on day 3. Patient number 1 died as a result of the graft failure and patient number 6 died on day 9 from a cerebrovascular accident with a viable graft (*Table 1*).

Discussion

Delayed primary closure of the abdominal wall as described has proved to be a useful technique in very small liver graft recipients who are too ill to await a graft of ideal size. As prospective assessment of liver size in cadaveric donors is rarely possible, most paediatric transplant units accept donors who are up to 1·5–2 times the weight of the recipient for whole liver grafts and a recipient:donor weight ratio of up to 1:5 or 1:6 for reduced-size grafting[1,4]. Although body-weight gives some indication of liver size, the size of segments two and three (together comprising the left lateral segment) varies greatly between donors of the same weight. Use of a simple weight ratio, therefore, may still result in a left lateral segmental graft proving to be too large. In the present group of children, transplantation of whole or reduced livers from much larger donors (ratio up to 1:8) was possible without detrimental effects on the graft or compromising the ventilatory ability of the recipient. Wound closure was usually achieved in two to three stages. After placement of the mesh, granulation tissue grew into it causing vascular adhesions of the mesh to the underlying liver and bowel loops. Therefore, frequent clinical assessment of the abdominal tension and ventilation was important to allow these repeated partial closure procedures to be performed as soon as possible. Mesh-related sepsis was not a problem.

In these patients, although it would be possible to cover the skin defect (with or without a mesh in place) with a split skin graft when healthy granulation tissue appears, this would probably result in an inferior cosmetic result.

This technique is based on the assumption that the oversized liver graft will reduce in size to fit the abdominal cavity of the recipient. The ability of the liver to enlarge[5,6] or shrink[6] spontaneously to the appropriate size has been particularly well documented in the serial volumetric studies in living related liver transplant recipients reported by Kawasaki *et al.*[6]. In the present series, the clinical impression of progressive reduction in liver size was substantiated by the ability finally to close the abdomen.

Delayed primary abdominal closure after liver transplantation in small children is feasible, probably because of spontaneous reduction in the graft size over the first few weeks. It is remarkably safe, gives good cosmetic results and may be of benefit in children otherwise at risk of graft infarction because of size disparity.

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British Journal of Surgery 1996, **83**, 1532–1536

Randomized comparison of the neuroendocrine response to laparoscopic cholecystectomy using either conventional or abdominal wall lift techniques

A.-M. KOIVUSALO, I. KELLOKUMPU*, M. SCHEININ†, I. TIKKANEN‡,
L. HALME and L. LINDGREN

*Departments of Anaesthesia and *Surgery, IV Department of Surgery, University of Helsinki, †Department of Pharmacology and Clinical Pharmacology, University of Turku, and ‡Department of Medicine, University of Helsinki, Minerva Institute, Helsinki, Finland*
Correspondence to: Dr A.-M. Koivusalo, Department of Anaesthesia, IV Department of Surgery, Kasarmikatu 11-13, FIN – 00 130 Helsinki, Finland

Increases in plasma renin activity and noradrenaline concentration occur in response to carbon dioxide insufflation during laparoscopic cholecystectomy. In a randomized study the conventional carbon dioxide pneumoperitoneum was compared with the abdominal wall lift method for laparoscopic cholecystectomy, with special reference to neuroendocrine changes and renal function. The total mean(s.d.) volume of carbon dioxide insufflated was 42(23) litres with the conventional method and 9(7) litres with abdominal wall lift ($P < 0·001$). Mean(s.d.) intra-abdominal pressure after 15 min of insufflation was 11(2) and 3(9) mmHg respectively ($P < 0·01$). In the conventional group mean(s.d.) plasma renin activity increased slightly from 5·5(2·1) to 6·1(2·0) ng ml^{-1} during the first 55 min of laparoscopic cholecystectomy. In the abdominal wall lift group plasma renin activity decreased from 5·3(2·7) to 3·8(0·9) ng ml^{-1} ($P < 0·01$ between the groups). Plasma antidiuretic hormone concentration increased similarly in both groups. Diuresis was significantly less with conventional pneumoperitoneum during the first 35 min of the operation compared with the abdominal wall lift method ($P < 0·001$). There were significant increases in plasma noradrenaline concentration in both groups ($P < 0·001$), but the increase was slightly higher in the conventional group during the first 15 min of insufflation. The abdominal wall lift method with minimal carbon dioxide insufflation was associated with smaller neuroendocrine responses and better preservation of renal function compared with conventional carbon dioxide pneumoperitoneum.

Pneumoperitoneum with carbon dioxide for laparoscopic surgery has disadvantages. Carbon dioxide insufflation causes respiratory acidosis[1] and significant haemodynamic changes, i.e. increases in arterial pressure and heart rate[2]. Also, increases in plasma concentrations of catecholamines and in plasma renin activity have been reported in response to carbon dioxide insufflation[3]. Increased intra-abdominal pressure (IAP) impairs renal function by compression of the kidneys[4,5]. The effect of pneumoperitoneum on renal function has not been evaluated.

The abdominal wall lift technique[6] has been introduced to avoid the adverse effects of increased IAP and excessive carbon dioxide load. With this method, IAP can be maintained at 1–4 mmHg and only 2–6 litres of carbon dioxide is needed.

The aim of this prospective randomized study was to compare conventional carbon dioxide pneumoperitoneum (IAP 12–15 mmHg) with the abdominal wall lift method for laparoscopic cholecystectomy with special reference to neuroendocrine response and renal function.

Patients and methods

Twenty-four patients with American Society of Anesthesiologists (ASA) grades I and II who had elective laparoscopic cholecystectomy were included. The study protocol was approved by the ethics committee of the hospital and informed consent was obtained. The patients were allocated randomly into two groups. Patients in group 1 had standard laparoscopic cholecystectomy with carbon dioxide insufflation at room temperature to achieve conventional pressure pneumoperitoneum. In group 2 the abdominal wall lift method was used with a minimal amount of carbon dioxide and lower IAP. A Hoffman's trocar was introduced under direct vision with a small carbon dioxide insufflation across and beneath the rectus abdominis muscle and the falciform ligament to lift the anterior abdominal wall[6] by 10–15 cm (*Fig. 1*). After initial carbon dioxide insufflation (1·5–1·8 litres) with the Hasson technique, carbon dioxide insufflation was kept minimal during the operation. If the surgeon was not satisfied with the view, extra carbon dioxide could be insufflated into the peritoneal cavity. All operations were performed by a single experienced surgeon (I.K.)

Patients were premedicated with oral diazepam 0·2 mg kg^{-1}. Before the induction of anaesthesia a fast volume loading was carried out with Ringer's acetate solution 8 ml kg^{-1} and during the operation 10 ml kg^{-1} h^{-1} was infused together with 6 per cent hydroxyethyl starch (Plasmafusin; Kabi Pharmacia, Halden, Norway). All patients received standardized anaesthesia induced with fentanyl 2 μg kg^{-1} h^{-1} followed by thiopentone 3–6 mg kg^{-1}. Muscle relaxation was achieved with vecuronium. Anaesthesia was maintained with isoflurane and analgesia was carried out with fentanyl 0·1 mg kg^{-1} h^{-1}. Patients were ventilated mechanically (Servo; Siemens Elema, Solna, Sweden) and end-tidal carbon dioxide was maintained within the normal range (4·5–5·1 per cent) (Cardiocap Ultima; Datex, Helsinki, Finland). Minute volume of ventilation was increased if needed.

After induction of anaesthesia the right subclavian vein was cannulated using the antecubital or internal jugular vein. A urinary bladder catheter, nasogastric tube and tympanic membrane temperature sensor (Mon-a-therm Tympanic; Mallincrodt Medical, Athlone, Ireland) were inserted. After the

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Presented in part to the Eighth European Anaesthesia Research Group Meeting Scientific Programme, Helsinki, Finland, August 1995
Paper accepted 27 December 1995

cannulations, a 20-min stabilization period was allowed. IAP and urine output were registered continuously. If the diuresis was less than 1 ml kg^{-1} h^{-1}, 100 ml of 15 per cent mannitol was given. If adequate urine output was still not achieved with mannitol, the patient was given frusemide 5 mg intravenously. The intraoperative fluid requirement and total amount of carbon dioxide insufflated were recorded.

Blood samples to determine the levels of adrenaline, noradrenaline, 3,4-dihydroxyphenylglycol (DHPG, a metabolite of noradrenaline), antidiuretic hormone (ADH), plasma renin activity, prolactin and serum lactate were collected from the subclavian catheter before skin incision and 15, 35 and 55 min after insufflation, and before extubation. Blood samples for catecholamines, DHPG, prolactin, plasma renin and ADH measurements were collected into prechilled polypropylene tubes containing ethylenediamine tetra-acetic acid and placed immediately on ice. The tubes were centrifuged at 0°C within 30 min and plasma was stored in polypropylene tubes at − 70°C until analysis. Plasma concentrations of catecholamines were measured with high-performance liquid chromatography with electrochemical detection[7]. The intra-assay coefficients of variation were approximately 2 per cent for noradrenaline, 10 per cent for adrenaline and 4 per cent for DHPG at physiological concentrations. Prolactin, plasma renin and ADH[8] were determined by radioimmunoassay.

Serum lactate concentration was also measured 30 min and 3 h after extubation. Serum urea and creatinine concentrations were measured before the operation and on the first postoperative day.

Diuresis was recorded up to 24 h after operation. When patients were discharged to the surgical ward the catheter was removed. The need for diuretics was recorded up to 24 h after the operation. Frusemide 10 mg was given intramuscularly if the patient was unable to void during the first 9 h on the ward.

Statistical evaluation was performed with analysis of variance (two-way ANOVA) for repeated measurements, with one between factor (treatment) and one within factor (time). Changes over time within a group were tested with one-way ANOVA for repeated measurements. If significant differences were found, further analysis was undertaken with Fisher's PLSD (least significant) test. Regression analysis was carried out between urine output, plasma renin activity and IAP. Statistical analysis was performed with StatView 512 software (Brain Power, Calabasas, California, USA). Single measurements were compared with Student's t test. $P<0{\cdot}05$ was considered statistically significant. Results are presented as mean(s.d.).

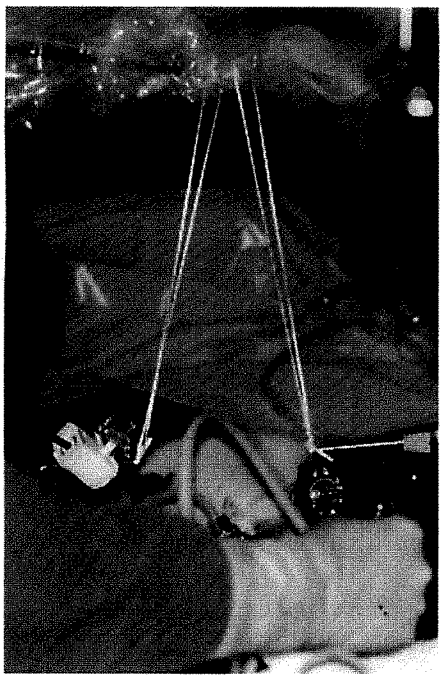

Fig. 1 Abdominal wall lift method with Hoffman's trocar

Results

The two groups were comparable with regard to demographic data and duration of operation (*Table 1*). There were no perioperative complications.

The total amount of carbon dioxide insufflated was 42(23) litres with the conventional technique and 9(7) litres with the abdominal wall lift method ($P<0{\cdot}001$). IAP at 15 min of insufflation was 11(2) and 3(9) mmHg respectively ($P<0{\cdot}01$). The duration of the operation was

Table 1 Patient details

	Group 1 (n = 12)	Group 2 (n = 12)
Mean (range) age (years)	49·7 (31–69)	48·5 (28–63)
Height (cm)*	167·8(8·1)	163·3(7·6)
Weight (kg)*	77·1(12·2)	70·8(7·6)
Sex ratio (F:M)	11:1	11:1
ASA grade I:II	8:4	6:6
Duration of operation (min)*	107·1(54·1)	85·7(19·6)

*Values are mean(s.d.). ASA, American Society of Anesthesiologists

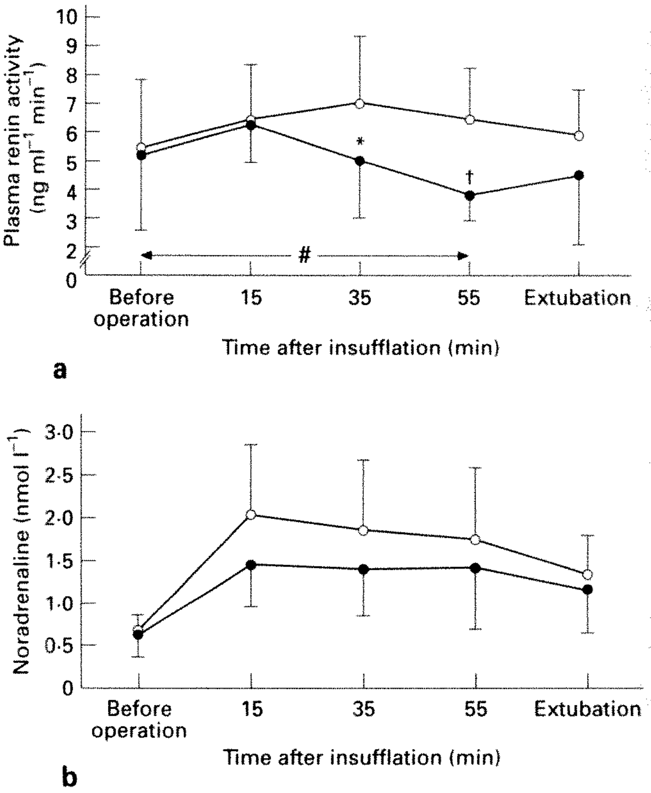

Fig. 2 a Plasma renin activity and **b** noradrenaline concentration during laparoscopic cholecystectomy. ○, Conventional pneumoperitoneum; ● abdominal wall lift. Values are mean(s.d.). *$P<0{\cdot}05$, †$P<0{\cdot}01$ *versus* conventional insufflation (one-way analysis of variance (ANOVA)). #$P<0{\cdot}05$ between the groups during the first 55 min (two-way ANOVA)

Table 2 Changes in adrenaline, 3,4-dihydroxyphenylglycol, prolactin and antidiuretic hormone concentrations during laparoscopic cholecystectomy

	Before operation	Carbon dioxide insufflation 15 min	35 min	55 min	At extubation
Adrenaline (nmol l^{-1})					
Group 1	0·04(0·05)	0·32(0·22)*	0·36(0·24)	0·21(0·14)	0·19(0·14)
Group 2	0·04(0·05)	0·35(0·24)*	0·28(0·17)	0·25(0·12)	0·22(0·22)
DHPG (nmol l^{-1})					
Group 1	4·53(1·33)	5·39(1·58)†	5·83(2·21)	6·13(2·82)	6·06(2·31)
Group 2	4·66(0·94)	4·88(1·16)	5·85(1·80)‡	5·74(1·80)	5·65(1·66)
Prolactin (m units l^{-1})					
Group 1	4110(1893)	4525(2013)	4044(1965)	3692(2108)	3255(2065)
Group 2	3820(2634)	5316(3643)§	3828(2150)‡	3781(2346)	3410(2208)
ADH (pg ml^{-1})					
Group 1	2·8(1·2)	83·0(72·2)§	52·8(58·8)	54·7(59·3)	32·9(27·5)
Group 2	3·4(2·3)	84·3(43·7)*	47·9(45·8)#	53·2(34·8)	22·8(18·8)¶

Values are mean(s.d.). DHPG, 3,4-dihydroxyphenyglycol; ADH, antidiuretic hormone. *$P < 0·001$, §$P < 0·01$, †$P < 0·05$ *versus* before operation; ‡$P < 0·01$, #$P < 0·05$ *versus* 15 min insufflation; ¶$P < 0·05$ *versus* 55 min insufflation (one-way analysis of variance)

Table 3 Diuresis and mean intra-abdominal pressure during the first 35 min of laparoscopic cholecystectomy

	Group 1	Group 2	P*
Diuresis (ml kg^{-1})	0·4(0·2)	2·1(1·5)	<0·001
Intra-abdominal pressure (mmHg)	11·0(1·7)	3·6(3·7)	<0·01

Values are mean(s.d.). *one-way analysis of variance

107(54) min in group 1 and 86(20) min in group 2 (P not significant).

There were no differences in end-tidal carbon dioxide concentration between the two groups. With the abdominal wall lift method there was no need to increase the minute volume of ventilation; with conventional insufflation a 15 per cent increase was needed.

In group 1 plasma renin activity increased slightly from 5·5(2·1) to 6·1(2·0) ng ml^{-1} min^{-1} during the first 55 min of insufflation. In group 2 plasma renin activity decreased from 5·3(2·7) to 3·8(0·9) ng ml^{-1} min^{-1} at 55 min ($P < 0·01$ between the groups). Plasma renin activity values followed different patterns in the two groups (two-way ANOVA, time × treatment, $P < 0·05$), and remained significantly lower throughout the operation in group 2 (*Fig. 2a*).

Similar marked increases were noted in plasma ADH concentration in both groups after 15 min of insufflation; the levels then decreased but remained above 20 pg ml^{-1} during the whole operation. The level of ADH fell towards normal more quickly after abdominal wall lift than with the conventional method ($P < 0·05$ in group 2 between 55 min and the end of the operation). The groups did not differ statistically (*Table 2*).

The concentration of noradrenaline in mixed venous plasma increased significantly in both groups ($P < 0·001$) but the increase tended to be larger in group 1 during the first 15 min of insufflation (P not significant) (*Fig. 2b*).

Plasma adrenaline levels were similarly increased during the first 15 min of operation in both groups ($P < 0·001$) (*Table 2*).

Plasma concentrations of DHPG increased slightly in both groups (*Table 2*), but there was no statistical difference between them.

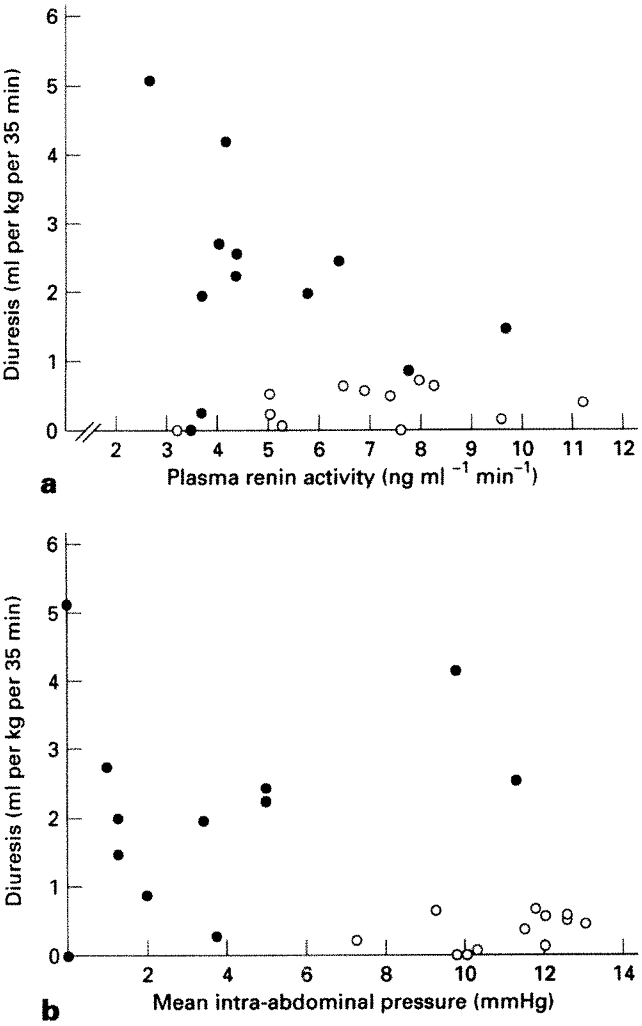

Fig. 3 Correlation between the urine output and **a** plasma renin activity and **b** intra-abdominal pressure during the first 35 min of laparoscopic cholecystectomy. ○, Conventional pneumoperitoneum; ●, abdominal wall lift. $r = -0·41$, $P < 0·05$ (correlation coefficient using XY-pairs)

Serum prolactin concentrations were not markedly influenced by either operation (*Table 2*).

Serum urea and creatinine levels were not different between the two groups before or after operation. Serum lactate levels were not altered during or after operation.

Tympanic membrane temperature decreased by 0·2(0)°C in group 1 but remained at the baseline level in group 2. The total amount of Ringer's acetate solution used was 1900(800) ml in group 1 and 1750(500) ml in group 2 (P not significant). The values for hydroxyethyl starch were 600(200) and 550(150) ml respectively (P not significant).

Diuresis during the first 35 min of insufflation was 0·4(0·2) ml kg^{-1} in the conventional group and 2·1(1·5) ml kg^{-1} with the abdominal wall lift method ($P<0{\cdot}001$). The simultaneous IAP values were significantly higher with the conventional than with the wall lift method ($P<0{\cdot}01$) (*Table 3*). During the following 30 min of insufflation these values were 0·3(0·4) and 0·5(0·5) ml kg^{-1} respectively (P not significant). Seven patients in group 1 and five in group 2 needed mannitol (P not significant). During the 3-h recovery room period diuresis was 7·8(4·0) ml kg^{-1} in group 1 and 6·7(4·0) ml kg^{-1} in group 2 (P not significant). Urine output was comparable in the two groups during the first 24 h after operation. No patient needed frusemide during the trial.

There was a negative correlation between urine output and plasma renin activity during the first 30 min of the operation ($r=-0{\cdot}41$, $P<0{\cdot}05$) and between urine output and mean IAP ($r=-0{\cdot}41$, $P<0{\cdot}05$) (*Fig. 3*).

Discussion

The abdominal wall lift method with minimal carbon dioxide insufflation for laparoscopic cholecystectomy was associated with smaller neuroendocrine responses than the conventional method. Urine output declined significantly during early conventional pneumoperitoneum but was generous with the abdominal wall lift method.

Renal function may deteriorate at an IAP of 10 mmHg[4,5]. An IAP of 15–20 mmHg causes renal impairment after laparotomy[9]. Insufflation of cool carbon dioxide into the abdominal cavity may also cause renal vasoconstriction[10]. In the present study diuresis during the first 30 min of insufflation was significantly less and plasma renin activity was significantly higher with the conventional method than with abdominal wall lift. The higher the plasma renin activity and IAP, the lower the urine output. Deterioration in urine output has been reported during carbon dioxide insufflation[11]. Impaired renal blood flow is an important activator of the renin–angiotensin–aldosterone (RAA) system[12]. An activated RAA system promotes renal vasoconstriction, mediated by angiotensin II. Angiotensin II is a potent regulator of systemic haemodynamics causing arteriolar vasoconstriction and release of catecholamines[13], and directs renal blood flow towards the medulla[14]. It is of importance that renal vasoconstriction is one of the main factors predisposing to decreased renal blood flow and acute tubular necrosis. Avoiding excessive carbon dioxide insufflation and high IAP with the abdominal wall lift method might be beneficial in patients with limited renal function because RAA is activated only slightly.

Induction of pneumoperitoneum resulted in a massive release of ADH in both groups. Unchanged prolactin levels, however, indicated that this was not a generalized non-specific neuroendocrine stress response. ADH concentration then decreased but remained over 20 pg ml^{-1}, considered to be the lowest plasma concentration that produces a vasoactive effect. Similar results have been reported in response to carbon dioxide insufflation[3]. Plasma concentration of ADH is raised following a variety of stresses; it increases after the start of surgery and may remain high for several days[15]. The main physiological role of ADH is to regulate diuresis following changes in serum osmolality[16,17]. All the present patients were given a similar high volume loading with iso-osmolar fluids. The clinical significance of the increase in ADH concentration may, however, be minor.

Despite the increase in plasma renin activity and ADH concentration during early insufflation, urine output seemed to recover during the day of operation. No changes were seen in serum urea concentration. These findings indicate that renal deterioration was transient.

Catecholamines, especially noradrenaline, are taken up selectively by the lungs[18,19]. Therefore venous blood was sampled from the superior vena cava to obtain a more accurate reflection of changes in catecholamine release. Increases in plasma renin activity and noradrenaline levels are considered to be a stress response to carbon dioxide insufflation[3]. The present results with regard to plasma renin activity, noradrenaline and adrenaline concentrations in patients having conventional pneumoperitoneum were similar to those reported by Joris and Lamy[3]. Plasma noradrenaline concentration increased more after conventional insufflation than with the abdominal wall lift method. Plasma adrenaline concentration increased similarly in both groups. Altogether, these increases were quite modest and did not indicate any major sympathoadrenal activation. A noradrenaline concentration of about ten times from basal is probably required to cause hormone-like actions. Anaesthetic use of opioid analgesia may have prevented major sympathoadrenal stress responses.

A 0·2°C decrease in core temperature is known to cause peripheral vasoconstriction[20]. Together with increased plasma renin activity and noradrenaline concentrations, cooling may have a harmful effect on renal blood flow. Warm carbon dioxide has been reported[10] to maintain urine output during laparoscopic surgery lasting up to 3 h. Also a totally gasless method[21] may protect renal function.

Carbon dioxide insufflation seems to be harmful to renal function. This may be a special problem for patients with borderline renal function; in those with a transplanted kidney, urine output declines to zero during pneumoperitoneum. The abdominal wall lift method may be ideal when laparoscopy is needed for patients with a transplanted kidney. Also patients with ASA grade IV may be treated successfully with this method.

Avoiding high IAP and excessive use of cool carbon dioxide might be beneficial to renal function by reducing neuroendocrine stress responses with the abdominal wall lift method.

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British Journal of Surgery 1996, 83, 1537–1542

Alterations in intestinal function in acute pancreatitis in an experimental model

X. D. WANG, Q. WANG, R. ANDERSSON and I. IHSE

Department of Surgery, Lund University Hospital, S-221 85 Lund, Sweden
Correspondence to: Dr R Andersson

Gastrointestinal tract failure may be involved in the development of systemic septic complications in acute pancreatitis. Systemic and intestinal circulation, intestinal permeability and absorptive function were evaluated in the early course of acute pancreatitis induced in rats by retrograde intraductal injection of 0·2 ml of 5 per cent sodium taurodeoxycholate and 0·4 nmol trypsin. A decrease in systemic arterial pressure and intestinal blood flow and an increase in intestinal permeability as measured by the leakage of ^{125}I-labelled human serum albumin from blood to lumen were noted in the distal ileum and colon, reaching statistically significant differences 6 h after induction of pancreatitis. The transport of small molecular markers (sodium fluorescein and ^{51}Cr-labelled ethylenediamine tetra-acetic acid) through the distal ileum and colon *in vitro* from the mucosal to the serosal site in Ussing chambers significantly increased in the early period (20–60 min) of incubation, while the passage of a macromolecular marker (ovalbumin) demonstrated a definite increase at 60–120 min of incubation. D-Xylose absorption from the gut lumen to the portal vein was significantly less in acute pancreatitis than after sham operation. Intravenous administration of the hydroxyl radical scavenger dimethylsulphoxide prevented the compromised intestinal permeability and gut absorptive capacity induced by acute pancreatitis, but did not affect the reduced arterial pressure and intestinal microcirculation. Cytotoxic oxygen-derived free radicals may contribute to the development of alterations in intestinal permeability and absorptive function found in the early stage of acute pancreatitis in the rat.

Bacterial infection and sepsis are major complications of acute pancreatitis. As the micro-organisms causative of pancreatic infection are generally of enteric origin, interest has lately been directed towards the role of the gut as the source of infection. In experimental pancreatitis, enteric bacterial translocation has been demonstrated, possibly related to a decrease in gut motility, to disruption of the endogenous bacterial ecology and to mucosal injury[1–3]. Marked alteration in intestinal permeability has been recognized as a characteristic of mucosal barrier injury in a variety of clinical conditions associated with a significant incidence of multiple organ failure[4–8]. Increased intestinal permeability has been considered to relate to pathological changes in the mucosa, disturbed ecology of the enteric microflora, compromised secretory immunoglobulin A synthesis, endotoxaemia and ischaemia–reperfusion[9,10]. Altered intestinal permeability may be associated with enteric bacterial overgrowth and translocation to extraintestinal sites.

The aim of the present experiments was to study intestinal barrier function by measuring permeability of the small intestine and colon both *in vivo* and *in vitro*, as well as gut absorptive capacity in the early stages of acute pancreatitis induced by retrograde intraductal injection of bile and trypsin. Furthermore, a possible role of oxygen-derived free radicals in the pathogenesis of the observed intestinal injury following acute pancreatitis was evaluated after pretreatment with an oxygen free radical scavenger, dimethylsulphoxide (DMSO).

Materials and methods

Animals

Adult male Sprague–Dawley rats (Møllegaard, Skensved, Denmark) weighing between 250 and 270 g were fed standard rat food (R_3; Astra-Ewos, Sodertalje, Sweden) and had free access to water. The animals were allowed to acclimatize for 4–6 days living in stainless steel mesh cages (three rats per cage) with a regimen of 12-h day–night cycle at a constant temperature of 22°C.

Induction of acute pancreatitis

The rats were operated on under aseptic conditions and general anaesthesia was induced and maintained with ether. Acute haemorrhagic pancreatitis was induced by intraductal administration of 0·2 ml 0·025 mol/l glycylglycin in sodium hydroxide buffer, pH 8·0, containing 5 per cent sodium taurodeoxycholate, and 0·4 nmol trypsin using an infusion pump at a speed of 0·04 ml/min, following occlusion of the proximal end of the common bile duct, and transduodenal cannulation of the biliary–pancreatic duct with a thin polyethylene catheter (0·66 mm external diameter; Portex, Hythe, UK)[11]. After the injection, the integrity of the common bile duct was restored. Sham operation (controls) was performed as above except for saline instead of bile infusion. All operations were completed within 10 min.

Systemic arterial pressure

Mean systemic arterial pressure was recorded in millimetres of mercury by cannulation of the femoral artery with a 0·75-mm external diameter tube (Portex) connected to a MINGOGRAF (Siemens–Elema, Erlangen, Germany). Cannulation was performed 1–2 h before the blood pressure measurements to reduce any effect of the operation.

Intestinal blood flow

Subserosal microcirculation of the small intestine and colon was evaluated with laser Doppler flowmetry (Perflux PE-2; Perimed, Stockholm, Sweden). This instrument uses 632·8-nm wavelength monochromic light emitted from a 2-mV helium–neon laser, with a penetration depth of 1 mm. The output from the flowmeter, the laser Doppler blood flow value of the intestinal subserosal circulation, was obtained from the display by the principle of Doppler shifts as described previously[12]. The cutoff frequency of the signal processing filter was set at 400 kHz for 3 s

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as a time constant of the output amplifier, which correlates to mean rather than pulsatile flow. The flow probe, the tip of the light conductor, was manoeuvred manually in a holder on the serosal surface with minimal pressure between the probe and the bowel wall. Six points were chosen randomly on the distal small intestine and colon for measurement of subserosal blood flow. This technique correlates well with submucosal blood flow by the hydrogen gas clearance technique[13].

Permeability of the intestine

The *in vivo* permeability of the proximal and distal small intestine, caecum and colon was assessed by quantitation of the blood-to-lumen movement of ^{125}I-labelled human serum albumin (Institutt for engergiteknikk, Kjeller, Norway). ^{125}I-labelled albumin (1 ml; mean(s.e.m.) radioactivity $1{\cdot}9(0{\cdot}3) \times 10^6$ c.p.m. per ml) was injected intravenously by cannulation of the femoral vein (external diameter 0·94 mm; Portex) 30 min before measurements. The animals were killed humanely and exsanguinated 30 min after the injection of radiolabelled albumin. The intestinal wall and content was separated and 3–5-cm long intestinal segments were obtained from the proximal jejunum (5–7 cm from the ligament of Treitz), the distal ileum (10–12 cm from the caecum), the caecum and the proximal colon (1–2 cm from the caecum). The radioactivity of blood and intestinal samples was measured in a γ counter (1272 Clinigamma; LKB, Wallac OY, Finland) and the samples were weighed Permeability of the intestinal barrier (from blood to lumen) and leakage of the radioisotope from blood into the intestinal tissues were expressed as isotopic flux[14,15], calculated from the ratio of radioactivity of samples (g) and blood (ml). Content of human serum albumin before and after the intravenous injections (labelling solution and rat serum) was measured by electroimmunoassay[16] with human serum albumin (Sigma, St Louis, Missouri, USA) as standard and using specific antisera to albumin (Dakopatts, Hägersten, Sweden).

In vitro permeability of the ileum and colon was evaluated in modified Ussing chambers by measuring the passage of ^{51}Cr-labelled ethylenediamine tetra-acetic acid (EDTA), sodium fluorescein and ovalbumin across the ileum and colon, which was considered to be more relevant to mucosal permeability *in vivo*. Segments (5 cm) of the ileum and colon were harvested and immersed at room temperature in modified Krebs–Ringer buffer, pH 7·4 (NaCl 110·0 mmol/l, $NaHCO_3$ 29·0 mmol/l, $CaCl_2$ 3·0 mmol/l, KCl 5·5 mmol/l, KH_2PO_4 1·4 mmol/l, sodium pyruvate 5·7 mmol/l and glucose 13·4 mmol/l), oxygenated with carbogen (95 per cent oxygen:5 per cent carbon dioxide). Each 5-cm segment was cut along the mesenteric border and mounted in a modified Ussing chamber[17] (Precision Instrument Design, Los Altos, California, USA) with an exposed area of 1·78 cm². The serosal and mucosal reservoirs were filled with 5 ml buffer, continuously oxygenated and circulated by gas lift at 37°C throughout the experimental procedure. After placing the sample, the buffer on the mucosal side was exchanged with 5 ml buffer containing the marker molecules. Samples (0·05 μl) were taken from the serosal reservoirs 20, 40, 60, 80, 100 and 120 min after incubation for marker analysis. Three markers were used to measure permeability of the isolated intestinal segments: sodium fluorescein 0·376 mg/ml (Merck, Germany; molecular weight 376 Da), ^{51}Cr-labelled EDTA 0·6 μCi/ml (NEN; Du Pont, God Hamburg, Germany; molecular weight 358 Da) and ovalbumin 5 mg/ml (Sigma; molecular weight 67 kDa). The radioactivity of ^{51}Cr-labelled EDTA was counted with a γ counter (LKB). The concentration of sodium fluorescein was measured by means of fluorescence measurement (Millipore CytoFluo 2300 Scanner with an NEC powermate 386/25S; CytoFluo, Stockholm, Sweden) at an excitation wavelength of 485 nm and an emission wavelength of 530 nm (25-nm bandwidth). Ovalbumin was measured by electroimmunoassay with ovalbumin (Sigma) as standard.

Assay of gut absorptive capacity

Gut absorptive capacity was evaluated by the 1-h D-xylose absorption test[18,19], performed 6 h after operation. Blood (0·3 ml) was sampled from the portal vein 1 h after oral administration of a 5 per cent solution (1 ml per 100 g body-weight) of D-xylose (0·5 g per kg body-weight; Sigma). The serum was separated, mixed with an equal volume of 20 per cent trichloracetic acid and kept on ice for 1 h before centrifugation. After the reaction of orcinol–ferric chloride reagent with the supernatant, the absorbance of the supernatant was measured spectrophotometrically at 660 μm in triplicate against a standard curve.

Experimental design

The rats were randomized to the following groups: (1) sham operation with intravenous (tail vein) saline; (2) acute pancreatitis with intravenous saline; (3) sham operation with intravenous DMSO; or (4) acute pancreatitis with intravenous DMSO. The hydroxyl radical scavenger DMSO (20 mg per kg body-weight) diluted in 1 ml saline was injected intravenously 1 h before operation. In each group rats were examined 3 h ($n = 6$ per group) and 6 h ($n = 14$ per group) after sham operation or induction of acute pancreatitis. Systemic arterial pressure and intestinal blood flow and absorptive capacity were measured, after which the intestine was removed and permeability assessed. Possible pathological alterations in the pancreatic parenchyma were examined both macroscopically and microscopically at the end of the experiments. The animals were anaesthetized during the experimental procedures and insertion of arterial and venous lines, and killed with an overdose of ether.

Statistical analysis

Results are expressed as mean(s.e.m.). Statistical analysis was performed with analysis of variance (one-way ANOVA) and Student's *t* test Blood flow measurements in the intestine were compared by non-parametric analysis (Wilcoxon signed rank test). A probability level of less than 0·05 was considered significant.

Results

No rat died during the perioperative period. A slightly pink ascitic fluid was present in animals with acute pancreatitis (mean(s.e.m.) 3·0(0·5) and 6·0(0·4) ml per rat 3 and 6 h after induction of acute pancreatitis). No macroscopic alterations were found in the gastrointestinal tract 3 or 6 h after induction of pancreatitis. However, definite oedema and bleeding foci appeared macroscopically in the pancreas and 30 and 60 per cent of the gland was necrotic on light microscopy after 3 and 6 h respectively. There was no significant difference in intestinal permeability and systemic haemodynamics after 3 h, although a trend towards increased intestinal permeability and decreased arterial pressure and intestinal blood flow was noted (data not shown).

Systemic blood pressure in animals with acute pancreatitis was significantly less than that in controls after 6 h ($P < 0{\cdot}05$; *Fig. 1*). Microcirculatory blood flow in the distal small intestine and colon was also significantly lower than in controls ($P < 0{\cdot}001$; *Fig. 2*). The leakage of radioactive albumin from the intestinal vessels to the intestinal lumen increased significantly in the distal small intestine and colon 6 h after induction of acute pancreatitis ($P < 0{\cdot}05$; *Fig. 3*). No difference in isotopic flux was noted in the proximal small intestinal wall and content, or caecal wall and content, nor in the distal small intestinal wall or colonic wall.

Animals having a sham operation together with DMSO administration showed similar levels as the controls of both systemic blood pressure and microcirculatory blood flow in the distal small intestine and colon. DMSO administration did not counteract the decrease in arterial

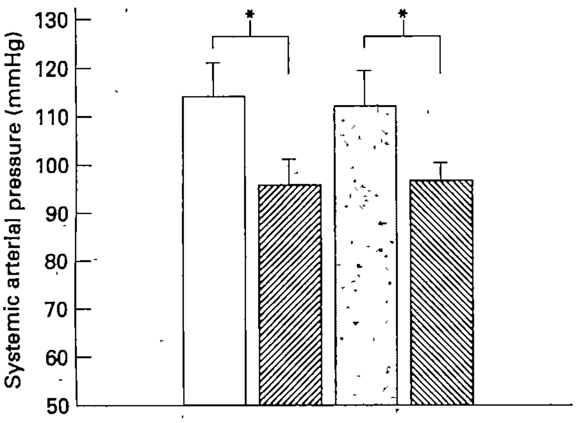

Fig. 1 Alterations in systemic mean(s.e.m.) arterial pressure 6 h after sham operation or induction of acute pancreatitis with saline or dimethylsulphoxide (DMSO). □, Sham operation; ▨, acute pancreatitis; ⬚, sham operation and DMSO; ▧, acute pancreatitis and DMSO ($n = 14$ per group). $^{*}P < 0{\cdot}05$ (Wilcoxon signed rank test)

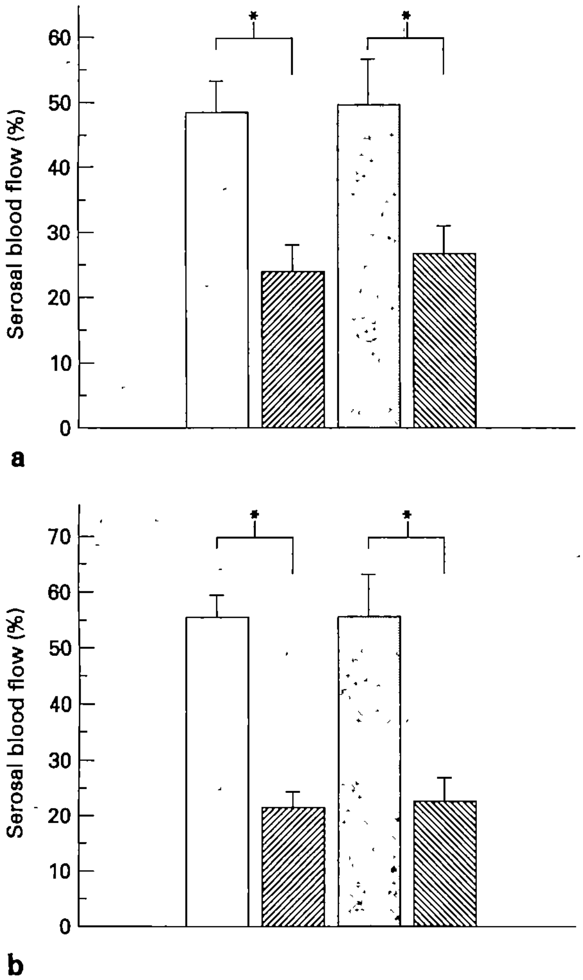

Fig. 2 Alterations in mean(s.e.m.) serosal blood flow in **a** the distal ileum and **b** the colon 6 h after sham operation or induction of acute pancreatitis, with saline or dimethylsulphoxide (DMSO). □, Sham operation; ▨, acute pancreatitis; ⬚, sham operation and DMSO; ▧, acute pancreatitis and DMSO ($n = 14$ per group). $^{*}P < 0{\cdot}001$ (Wilcoxon signed rank test)

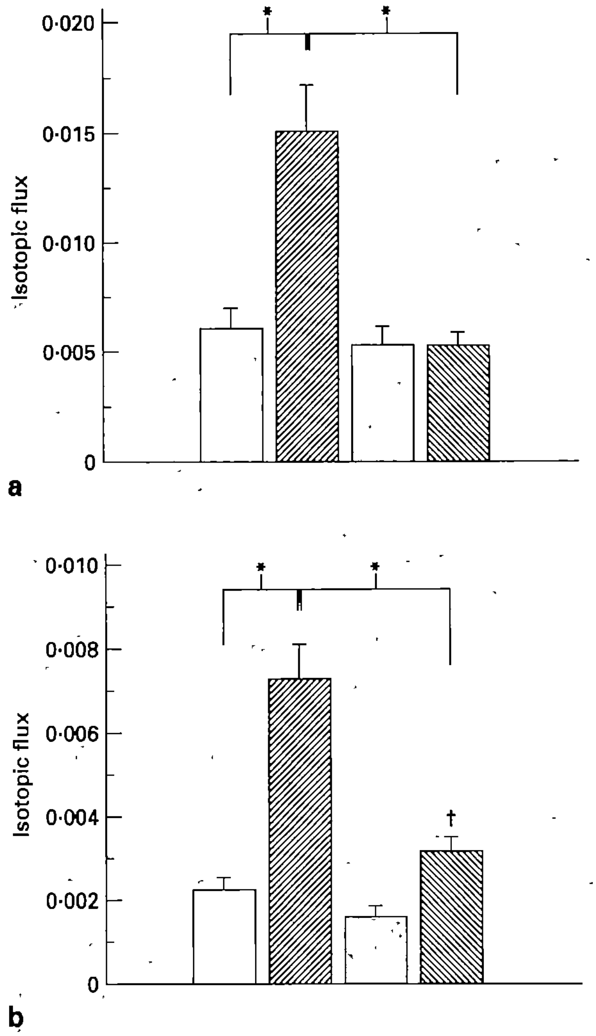

Fig. 3 Alterations in mean(s.e.m.) isotopic flux of ^{125}I-labelled human serum albumin into **a** the distal small intestinal lumen and **b** the colonic lumen 6 h after sham operation or induction of acute pancreatitis with saline or dimethylsulphoxide (DMSO). □, Sham operation; ▨, acute pancreatitis; ⬚, sham operation and DMSO; ▧, acute pancreatitis and DMSO ($n = 14$ per group). $^{*}P < 0{\cdot}05$ (ANOVA, student's *t* test)

blood pressure or in blood flow in the ileum and colon in animals with pancreatitis, which in fact was significantly lower than that in controls and no different from that in animals with acute pancreatitis with no DMSO. However, the leakage of radioactive albumin from the ileal and colonic vessels to the intestinal lumen decreased significantly in animals given DMSO, since isotopic flux to the ileum and colon differed statistically from that in the group with acute pancreatitis alone ($P < 0{\cdot}05$; *Fig. 3*).

An increase in the intestinal passage of fluorescein, ^{51}Cr-labelled EDTA and ovalbumin was seen in both the ileum and colon in animals with acute pancreatitis without DMSO but not in those with DMSO. An increased passage of fluorescein from the mucosal to the serosal reservoir was found in animals with acute pancreatitis, in the ileum after 20, 40 and 60 min, and in the colon after 40 min (*Fig. 4*). The transport of fluorescein over ileal segments was significantly lower in the group with acute pancreatitis treated with DMSO than in the group with

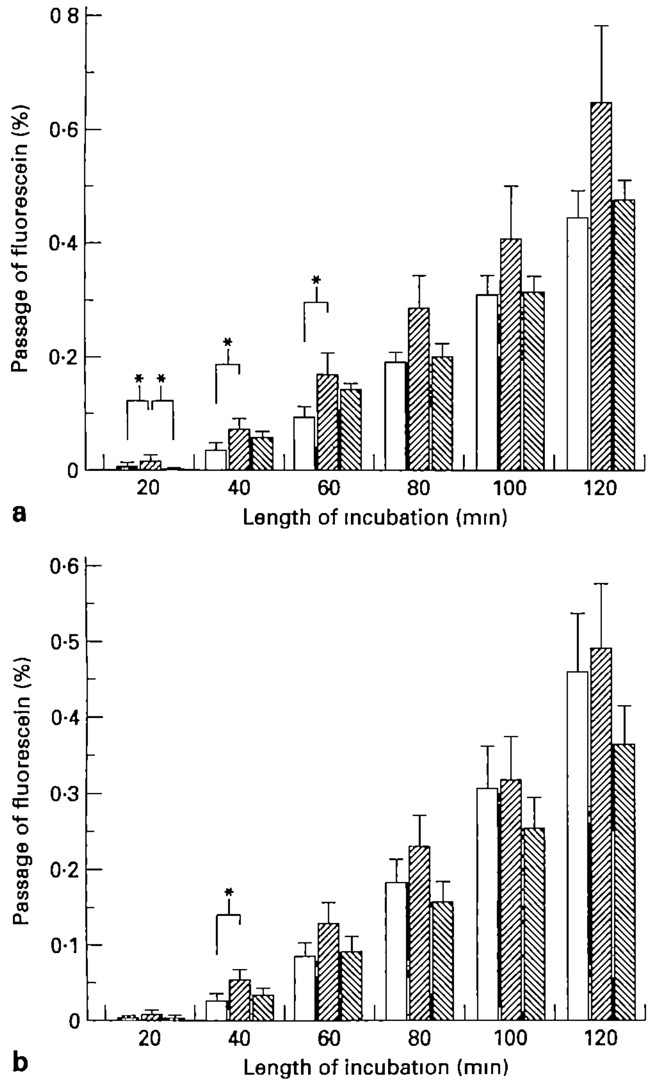

Fig. 4 Passage of sodium fluorescein from the mucosal to serosal site in the Ussing chamber *in vitro* within 120 min of incubation through samples from **a** the distal ileum and **b** the colon harvested 6 h after sham operation (□, controls with both saline and dimethylsulphoxide (DMSO)) or induction of acute pancreatitis with saline (▨) or DMSO (▧) ($n = 14$ per group) Values are mean(s.e.m.). $^*P < 0{\cdot}05$ (ANOVA, student's t test)

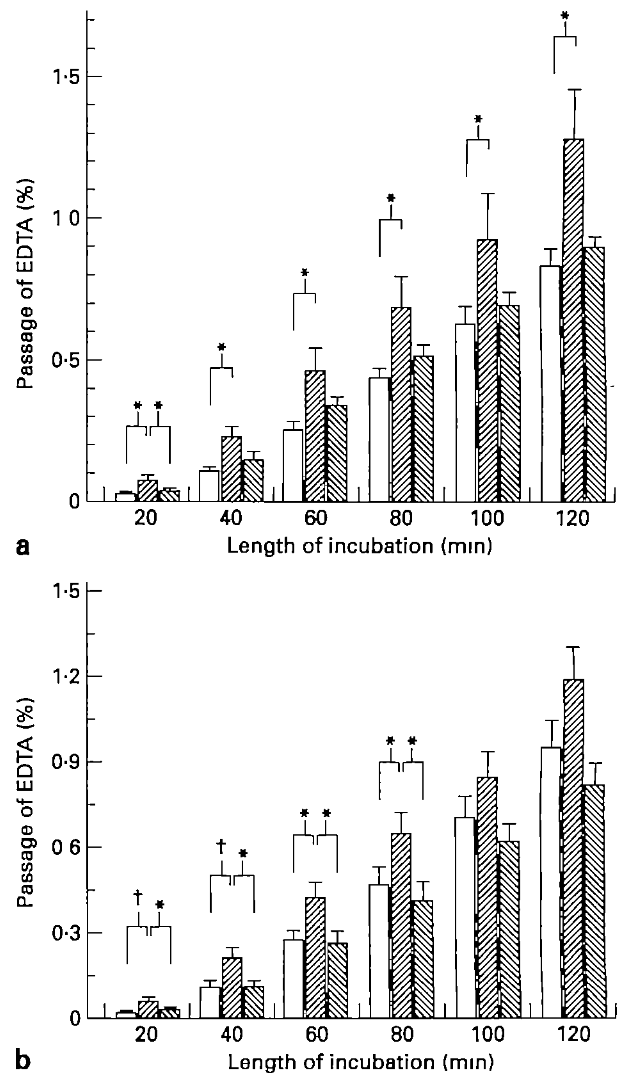

Fig. 5 Passage of ^{51}Cr-labelled ethylenediamine tetra-acetic acid (EDTA) from the mucosal to serosal site in the Ussing chamber *in vitro* within 120 min of incubation through samples from **a** the distal ileum and **b** the colon harvested 6 h after sham operation (□, controls with both saline and dimethylsulphoxide (DMSO)) or induction of acute pancreatitis with saline (▨) or DMSO (▧) ($n = 14$ per group). Values are mean(s.e.m.) $^*P < 0{\cdot}05$, $^†P < 0{\cdot}01$ (ANOVA, student's t test)

acute pancreatitis without DMSO at 20 min after incubation (*Fig. 4*). Passage of ^{51}Cr-labelled EDTA through the ileum was significantly higher in acute pancreatitis without DMSO than in controls for all periods of incubation, and higher than in acute pancreatitis with DMSO at 20 min (*Fig. 5*). A significant increase in the transport of radioactive EDTA through the colon following acute pancreatitis alone was noted 20–80 min after incubation, differing from both controls and animals with acute pancreatitis with DMSO administration (*Fig. 5*). Ovalbumin transport through the ileum and colon increased significantly in acute pancreatitis alone compared with controls from 80 to 120 min and from 60 to 120 min respectively. No difference was noted between animals with acute pancreatitis and DMSO and those undergoing sham operation. DMSO treatment abolished the increased ovalbumin transport after pancreatitis (*Fig. 6*).

Mean(s.e.m.) concentration of D-xylose in the portal vein of animals with acute pancreatitis (0·24(0·05) mmol/l) was significantly lower than that in controls, with or without DMSO (0·34(0·48) and 0·36(0·06) mmol/l respectively, $P < 0{\cdot}05$). DMSO administration prevented the changes in D-xylose absorption in animals with acute pancreatitis (0·31(0·04) mmol/l).

Discussion

The gastrointestinal epithelium, which is normally selectively permeable[20], may, under various conditions, undergo permeability changes that may proceed to gut

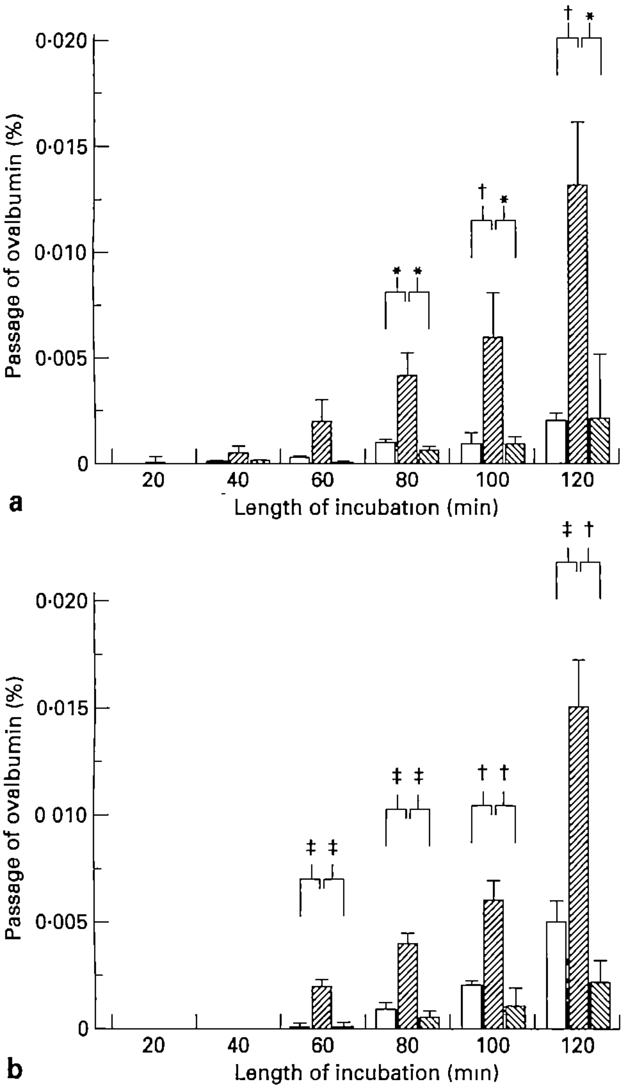

Fig. 6 Passage of ovalbumin from the mucosal to serosal site in the Ussing chamber *in vitro* within 120 min of incubation through samples from **a** the distal ileum and **b** the colon harvested 6 h after sham operation (□, controls with both saline and dimethylsulphoxide (DMSO)) or induction of acute pancreatitis with saline (▨) or DMSO (▧) ($n = 14$ per group). Values are mean(s.e.m.) $*P<0·05$, $†P<0·01$, $‡P<0·001$ (ANOVA, student's t test)

barrier failure[4–8]. The gut barrier comprises a number of sub-barriers, including the unstirred water layer, the mucus coat, the brush border cell membrane, the intercellular junctional areas, the epithelial layer and the gut-associated lymphatic tissue, of which the epithelial layer covering the intestinal villi forms the most superficial physical part[21]. In the present study the permeability of the intestinal barrier, as measured by the leakage of radioactive albumin from the intestinal blood vessels to the lumen of the gastrointestinal tract, was considered to reflect two main sub-barriers: the capillary endothelial and mucosal epithelial layers (mucosal barrier). A marked increase in permeability of the distal small intestine and colon was observed in animals with acute pancreatitis, although the underlying mechanisms remain unclear.

The Ussing chamber has been used as an *in vitro* system to evaluate the transmucosal transport of various molecular markers. Previous histological (light and electron microscopy) and functional (cellular viability) studies have shown no changes in the mucosa and an intact epithelium for up to 2 h[22]. The intercellular pathway is a major route of permeation of the intestinal epithelium for water, and water-soluble nutrients and compounds[23]. The tight junctions and their structural strands are supposed to be the most important factor for the limitation and regulation of penetration across the paracellular junctions[24]. The transport of EDTA and sodium fluorescein through the ileum and colon significantly increased initially during the incubation period (from 20 min), while an increased passage of ovalbumin occurred later (from 60 min).

The intestinal transport of D-xylose from the lumen to the portal vein represents gut absorptive capacity and reflects the transfer function of the brush border membrane. The primary mechanism for the absorption of the D-xylose, as for glucose, is transport across the brush border membrane of the mucosal cells by an active energy-requiring process in the presence of a specific transport protein and sodium ions, although the absorptive rate from the intestinal lumen is only 15 per cent that of glucose[25]. The gut absorptive capacity was reduced in acute pancreatitis, indicating that the transport function of the brush border membrane is impaired. This is probably caused by a decrease in brush border membrane Na^+–K^+ adenosine 5′-triphosphatase activity[26]. The decrease in gut absorption capacity is unlikely to result from an increase in intestinal transit, because the intestinal transit time is delayed after induction of acute pancreatitis[1].

The pathophysiological mechanism(s) responsible for changes in intestinal permeability and absorption in acute pancreatitis may be associated with hypovolaemia and reduced mesenteric–intestinal blood flow. Previous studies have demonstrated increased intestinal permeability and a diminished gut absorptive capacity during systemic and intestinal ischaemia[5–7]. In the present study subserosal blood flow in the intestine was used to reflect the mucosal tissue microcirculation, because a definite relationship exists between serosal and mucosal blood flow[13,27]. Alterations in gut function after induction of acute pancreatitis were noted concomitantly with the occurrence of intestinal ischaemia. DMSO prevented the disturbances in intestinal permeability and absorption without improving the systemic and local haemodynamic situation. These results show that DMSO does not act as a plasma expander to protect against mucosal injury by increasing the circulatory volume, and that reduced intestinal blood flow by itself does not seem to be a primary factor directly affecting gut permeability and absorption.

Persistent alterations in intestinal permeability after ischaemia and reperfusion have been suggested to be related to neutrophil aggregation, adherence, transmigration and oxygen-derived free radical release, which may contribute to dissociation of intercellular junctions, brush border membrane dysfunction and mucosal barrier failure[28]. Oxygen-derived free radicals produced locally during haemorrhagic shock inhibit splanchnic prostaglandin synthesis. This may be responsible for the decreased splanchnic blood flow. Experimental findings imply that oxygen-derived free radicals may play an important role in the pathogenesis of acute pancreatitis. The oxidative stress, defined as potential damage from an excess of oxidants over antioxidants, has been demonstrated as an early phenomenon characteristic of acute experimental pancreatitis[11]. In the present study the use of the hydroxyl radical scavenger, DMSO, markedly reduced intestinal permeability changes *in vivo* and *in vitro*. Furthermore DMSO administration maintained brush border membrane function in acute pancreatitis, probably by neutralizing cytotoxic oxygen-derived free radicals[29]. The present findings are supported by previous experiments in which intravenous administration of DMSO before haemorrhagic shock prevented intestinal mucosal injury and gut origin sepsis[30].

A possible mechanism to explain failure of the intestinal barrier in experimental acute pancreatitis is that systemic and local ischaemia–reperfusion injury reduces the mucosal microcirculation, compromises oxygen delivery and results in insufficient energy production. This may reduce the regeneration of adenosine 5′-triphosphate by oxidative phosphorylation in enterocytes, which causes release of cytotoxic oxygen-derived free radicals by activated leucocytes, macrophages and/or intestinal capillary endothelial cells[31]. Xanthine dehydrogenase–oxidase activity exists mainly in the mucosal layer, with an increasing gradient of activity from the villus base to the villus top. Excessive production of oxygen-derived free radicals may induce alterations in intestinal permeability and absorption in acute pancreatitis by effects of lysosomal proteases and eicosanoids released by stimulated leucocytes, macrophages, dendritic cells and antigen-presenting cells in the mucosa, and by lipid peroxidation of cell membranes[32]. It could also be that the stabilizing effect of DMSO on alterations in intestinal permeability and adsorption may be exerted by extraintestinal mechanisms.

In conclusion, intestinal permeability increased and gut absorptive capacity decreased in the early phase after induction of acute pancreatitis, concomitant with systemic hypovolaemia and intestinal ischaemia. Intravenous administration of DMSO, a hydroxyl radical scavenger, prevented changes in intestinal permeability and absorption without influencing the systemic or intestinal circulation.

Acknowledgements

This study was supported by grants from the Swedish Medical Research Council (grant nos 17X-03012 and B95-17X-11236) and the Medical Faculty, Lund University, Sweden.

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British Journal of Surgery 1996, 83, 1543

Case report

Laparoscopic cholecystectomy in a patient receiving continuous ambulatory peritoneal dialysis

A. M. LALE, T. J. WHEATLEY and
M. L. NICHOLSON
Department of Surgery, Leicester General Hospital, Leicester LE5 4PW, UK
Correspondence to: Mr M L Nicholson

Minimally invasive surgical techniques cause little disruption of the abdominal wall and peritoneum and have clear potential benefits in patients receiving continuous ambulatory peritoneal dialysis (CAPD). The presence of a peritoneal catheter allows the creation of a pneumoperitoneum completely non-invasively.

Case report

A 64-year-old man maintained on CAPD for end-stage renal failure secondary to hypertension presented with two episodes of acute cholecystitis. Ultrasonographic scanning confirmed the diagnosis of gallstones and demonstrated thickening of the gallbladder wall. Elective laparoscopic cholecystectomy was performed 3 months later. All peritoneal fluid was drained from the abdomen before operation A pneumoperitoneum was created by connecting the carbon dioxide insufflator directly to the CAPD catheter. The camera was introduced through a cannula placed just above the umbilicus. Dissection instruments were placed through a 10-mm epigastric cannula, and 5-mm cannulas in the mid-clavicular and anterior axillary lines were also used. The gallbladder was dissected using diathermy and was removed through the umbilical port. The muscle layers of the epigastric and umbilical ports were carefully closed using a 0 polyglactin suture on a J-shaped needle

Peritoneal dialysis was re-established within 4 h of operation, using a cycling peritoneal dialysis machine with low-volume (500 ml) exchanges for the first 24 h. The usual protocol of four daily 1-litre exchanges was reinstituted on the second day after operation, and the patient was discharged at that time The peritoneal fluid was completely free of blood or bile and there was no fluid leakage from any wounds.

Paper accepted 10 January 1996

Discussion

Laparoscopic cholecystectomy is associated with less pain after operation, shorter recovery times and improved cosmesis[1 2]. Laparoscopic cholecystectomy offers other important advantages in patients receiving CAPD. Open abdominal operations in these patients disrupt the peritoneum with the risk of postoperative dialysis fluid leakage[3]. At best this necessitates a temporary transfer to haemodialysis, which means the placement of a temporary central venous access catheter and utilizes haemodialysis resources at a time when these are already at saturation point. Occasionally, open operation leads to obliteration of the peritoneal cavity and permanent transfer to haemodialysis.

The presence of a CAPD catheter allows the creation of a pneumoperitoneum completely non-invasively, thus avoiding the risks associated with the introduction of the first trocar and cannula. CAPD can be re-established immediately after laparoscopic cholecystectomy, and a protracted in-patient stay is not necessary. The minimal access approach is likely to cause less bleeding; even if this does occur, the CAPD catheter provides both a diagnostic 'window' into the peritoneal cavity and a means of washing out collections of blood or bile. Some attention to detail is required to avoid problems: careful placement of the stab incisions to avoid the CAPD catheter track, suture closure of the ports and the use of relatively low volumes of dialysis fluid early in the postoperative course are suggested.

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British Journal of Surgery 1996, 83, 1544–1547

Audit of general practitioner referrals to a surgical assessment unit: new methods to improve the efficiency of the acute surgical service

K. A. DOOKERAN, I. BAIN and V. MOSHAKIS

Department of Surgery, George Eliot Hospital, Nuneaton CV10 7DJ, UK
Correspondence to: Mr K. A. Dookeran, Department of Surgery, 300 Kaufmann Building, 3471 Fifth Avenue, Pittsburgh, Pennsylvania 15213-3221, USA

A total of 653 referrals from general practitioners to an acute surgical service were audited prospectively over a period of 4 months. Middle-grade staff accepting these referrals were able to deal with 182 (27·9 per cent) of these calls without surgical admission. A further 189 (28·9 per cent) referrals were seen on a surgical assessment unit and were not admitted to a surgical ward. The resultant cost saving was approximately £10 000. This confirms that the ready provision of an experienced surgical opinion in combination with early assessment can reduce the number of unnecessary acute surgical admissions referred from general practitioners.

One function of primary care-based health systems is screening of emergencies in the community by family or general practitioners (GPs). Patients needing hospital care may then be referred directly to the appropriate service. It is unclear whether high referral rates may be due to ineffective screening procedures; however, this can result in substantial workload and expenditure for the receiving hospital service.

A prospective audit has been reported[1] of the mechanism of referral of acute surgical admissions, which involved the duty preregistration house officer (HO) accepting telephone referrals and arranging admission for acutely ill surgical patients referred by GPs. This audit revealed that 41 per cent of such admissions were inappropriate, and the estimated cost of these admissions was substantial. The study also revealed the need for an experienced surgical opinion in almost half of patients considered inappropriate for admission.

Surgical audit has demonstrated that urgent admissions reduce the number of available beds and decrease the rate of treatment of elective patients, and thereby reduce the efficiency of the surgical service[2]. Improved assessment mechanisms in the accident and emergency department have been shown to reduce the number of acute surgical referrals[3].

These considerations prompted a reorganization of the admissions procedure provided for GP referrals by the acute surgical service in this hospital. GPs' calls were taken by the registrar or senior house officer (SHO) on call; this allowed screening of referrals and provision of advice where appropriate, reducing the number of patients who had to be seen urgently. An experienced surgical opinion was provided for early assessment and triage of patients in a surgical assessment unit (SAU). The aim of these measures was to decrease the number of unnecessary surgical admissions. This study was a prospective audit of these methods.

Patients and methods

Between 2 September 1993 and 31 December 1993, all acutely ill patients referred by GPs to the acute general surgical service at this hospital were audited prospectively. The service comprised four consultant surgeons, two registrars, two SHOs and five preregistration HOs based on two adult wards with a total of 53 beds. Children under the age of 14 years were admitted to a separate paediatric ward and were not included in the study. The SAU was created by the allocation of a bay in the accident and emergency department at no cost to the surgical service, for the purpose of the study. No structural changes were required. The SAU provided six beds which were included in the bed count (i.e. no new beds were created and six adult beds were closed) The daily duty on-call team consisted of a consultant, registrar or SHO, and HO.

The following groups of patients were excluded from the study. patients referred from the accident and emergency department, those admitted from outpatient clinics and domiciliary visits, and those who were admitted electively. All urgent GP referrals were seen in the SAU. Patients referred after 23.00 hours were admitted directly to the surgical wards for 2 months of the study when the SAU closed due to lack of nursing staff.

Referral calls were taken and assessed by the registrar on call. Calls that led to referral to the surgical outpatient clinic, other specialties, or simple surgical advice were recorded for the study For all other GP calls, when it was decided that the patient needed surgical assessment, the patient was seen in the SAU

An audit form was completed prospectively for each patient and included demographic details; time taken to see the patient, and the grade of doctor admitting; the reason for referral; details of the accompanying GP letter; referral category (*Table 1*); clinical diagnosis; investigations, treatment and outcome.

Patients were assessed by the surgeon on call (registrar or SHO) who decided which patients should be admitted to the surgical wards, if admission was not required, the registrar decided which referral category the patient fulfilled, what investigations were needed, which patients should be referred to other specialties or discharged, and for the latter what follow-up was required. This process did not usually involve the consultant. Patients who were discharged were provided with a detailed

Table 1 Categories of referrals for which surgical admission was considered inappropriate

1	Admission necessary but to a different specialty
2	Surgical opinion necessary today but not admission
3	Outpatient appointment required (urgent, 1 week or less)
4	Outpatient appointment required (routine)
5	Surgical advice via telephone required
6	No opinion or advice necessary

Paper accepted 7 January 1996

Table 2 Cost estimates used to calculate expenditure

Item	Cost (£)
Bed stay per day	130·00
Staff (two 'E' grade and two 'D' grade nurses early shift, one 'E' grade and one 'D' grade nurse late shift; two 'E' grade nurses night shift, 24-h cover at £345·73 per day) hourly rate	14·40
Urgent investigations	
Full blood count	2·51
Urea and electrolytes	1·94
Glucose	1·84
Amylase	7·02
Urine microscopy	2·85
Electrocardiography	7·00
Chest and abdominal radiography (each)	32·42
Ultrasonography of the abdomen	51·05
Pharmacy prescriptions (per head approximately)	3·00
Consumables (per head approximately)	2·43

discharge letter, and a copy was posted to their GP. The audit process did not interfere with clinical judgement or patient care.

The approximate values of items used to calculate the costs of the SAU are listed in *Table 2*. The cost of nursing staff for six adult beds on the SAU was calculated by determining the hourly rate for 24-h cover multiplied by the actual time for which nurses covered the unit (i.e. time of patient entry to SAU to time of discharge or ward transfer). Nurses were utilized on other wards when patients were not present in the SAU and that cost was allocated to the specific service. The costs of investigations and pharmacy prescriptions were calculated by multiplying the item cost by the number of patients requiring the item. Intravenous lines and cannulas, syringes, needles, gauze sponges, cleaning agents, disposable proctoscopes and sigmoidoscopes, thermometers and sphygmomanometers, and so forth are listed as consumables; this cost was calculated by summation of the costs for individual items used during the study period. Routine operating and outpatient commitments were also covered by staff-grade surgeons who were members of the surgical team without on-call commitment; this is a long-standing arrangement and no additional staff were required.

Results

A total of 653 referral calls requesting admission for acutely ill patients were received from local GPs during the 4-month period of the study. Of these, 182 calls (27·9 per cent) were dealt with by advice only and 471 patients (72·1 per cent) were seen for assessment in the SAU. There were 240 men (51·0 per cent, age range 14–91 years) and 231 women (49·0 per cent, age range 14–111 years).

Many patients (305 of 471, 64·8 per cent) were admitted during normal working hours (8.00–17.00 hours); 25·3 per cent (119 of 471) were admitted between 17.00 and 23.00 hours, and only 9·9 per cent (47 of 471) were admitted between 23.00 and 8.00 hours. This last figure was artificially low, because the SAU was closed at night for half of the study period.

Some 71·8 per cent (338 of 471 patients) were seen by a doctor within 30 min of admission, and a further 80 (17·0 per cent) were seen within 1 h of admission; only 53 (11·2 per cent) were first seen by medical staff more than 1 h after admission. The admitting doctor was a HO in 336 cases (71·3 per cent), a registrar in 131 (27·8 per cent) and a consultant in only four (0·8 per cent). Some 294 patients (62·4 per cent) seen in the SAU were admitted to a ward or discharged within 3 h of being seen.

Forty-five patients (9·6 per cent) arrived in the SAU without a referral call; 163 (34·6 per cent) had no accompanying GP referral letter. Of the 308 GP referral letters 76 (24·7 per cent) did not indicate the presenting complaint or history, 115 (37·3 per cent) did not indicate regular prescriptions that patients were taking, 134 (43·5 per cent) did not indicate significant past medical history, 141 (45·8 per cent) did not indicate significant symptoms and signs present in other systems, 48 (15·6 per cent) did not indicate the presence of a significant social problem and 56 (18·2 per cent) did not indicate the results of the GP's clinical examination.

A total of 189 referrals (40·1 per cent) seen in the SAU were considered to be inappropriate for admission to a surgical ward (*Fig. 1*). Some 171 patients (90·5 per cent) were sent home and 18 (9·5 per cent) were referred to other specialties (11 to gynaecology, five to medicine, one to orthopaedics and one to plastic surgery). Of these 189 patients, 119 (63·0 per cent) required a surgical opinion immediately (18 needing admission to a different specialty and 101 requiring a surgical opinion without admission). Comparison of GP and surgical diagnoses for these patients revealed that many (102 of 189, 54·0 per cent) were referred with abdominal pain; for this group of patients almost half (57 of 102) had no surgical problem, and almost one-quarter (28 of 102) had constipation or a urinary tract infection.

The cost of nursing staff for the SAU amounted to 1235 h of nursing time, which at £14·40 per h amounts to £17 784. However, acute GP referrals to the SAU

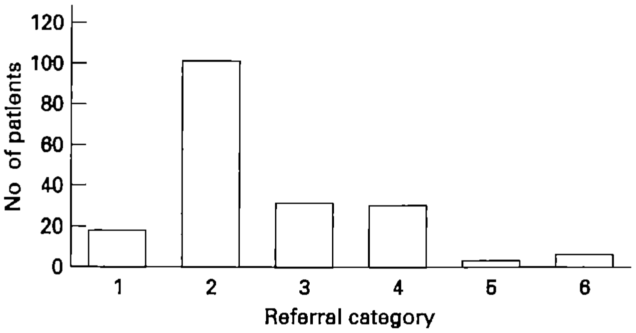

Fig. 1 Patients who were considered to be inappropriate for surgical admission. The referral category is defined in *Table 1*

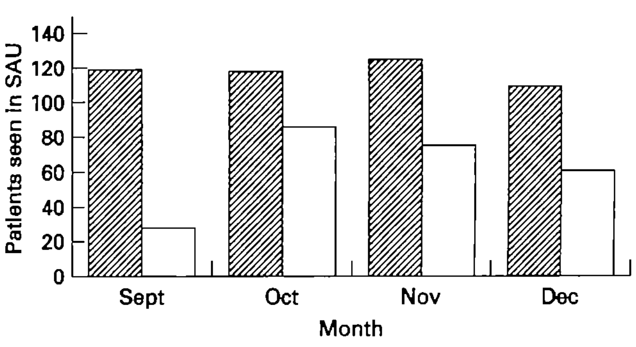

Fig. 2 Distribution of acute surgical patients seen in the surgical assessment unit (SAU) during the study period. ▨, General practitioner referral; ☐, other referral

accounted for only 65·3 per cent (471 of 721) of patients seen there (*Fig. 2*); accordingly, this amounts to £11 612·95 (i.e. 0·653 × £17 784) for nursing for these patients. Investigations and prescriptions for these patients cost a further £1468·73, and consumables cost a further £1144·53. This amounts to a total expenditure of £14 226 for the running cost of the SAU. If the 189 referrals seen in the SAU and discharged because they were considered inappropriate for admission to a surgical ward were hypothetically admitted for a minimum of a 1-night stay in hospital at £130 per bed, a cost of £24 570 (i.e. 189 × £130) would be incurred. If the running costs for the SAU were subtracted from this figure (i.e. £24 570 – £14 226), the difference of £10 344 is potential revenue saved.

Discussion

The evaluation and treatment of patients referred acutely by GPs account for most of the workload of the acute surgical service (*Fig. 2*) at this hospital. Inefficiencies of the admissions procedure as practised before this study have been demonstrated at this hospital and elsewhere [1]. The new methods implemented here are aimed directl at reducing the number of unnecessary acute surgical admissions and, as far as the authors are aware, this study is unique in attempting to improve the resource management and efficiency of the acute surgical service.

In addition to the 182 patients who were not considered appropriate for acute surgical assessment, 70 (referral categories 3–6 in *Fig. 1*) assessed on the SAU in retrospect did not need an acute visit. Hence a total of 38·6 per cent of all GP referrals did not need to be seen in the SAU. This confirms that screening of GP calls by an experienced member of the duty surgical team helps to reduce the number of urgent admissions; however, because 27·8 per cent (70 of 252) of these patients were actually seen in the SAU, there is potential for even further reduction. In addition, many patients seen in the SAU who did not need admission to a ward were seen for abdominal pain (102 of 189); however, most patients with this presenting complaint (85 of 102) were found to have no surgical problem, or constipation or urinary tract infection. These diagnoses usually do not require an immediate surgical evaluation and support the contention that the number of patients seen in the SAU could be further reduced.

Many patients (64·8 per cent) were admitted to the SAU during normal working hours. Special efforts were made to take GP calls and to see patients in the SAU as soon as possible. This was facilitated by registrars having fixed call days with their units, with other members of staff helping mainly with the routine work in clinics and operating theatres, thereby releasing the 'on duty' middle-grade staff to concentrate on GP referrals. Although no additional staff were required to accomplish this arrangement, consultants and staff-grade surgeons were often left to cover routine commitments alone. Although the HO was the admitting officer in 71·3 per cent of cases, both experienced and junior staff were already aware of impending admission, and investigations were usually ordered by the registrar.

Patients had the benefit of being put into a hospital bed in an area designated for surgical assessment, staffed with surgical ward nurses whose sole focus was to expedite management. The location of the SAU adjacent to the radiology department, accident and emergency department, pathology laboratory and operating theatres also expedited investigations and management. This meant that doctors spent less time waiting for results, and could use their time more effectively. This setting was also more efficient for resuscitation of acutely ill patients who required high-dependency care. Once a decision to admit had been made, the patient could go straight to the operating theatre or ward as required, prepared with treatment initiated, and administrative information already processed. Most patients were transferred within 3 h, which allowed the SAU to function as intended. Management on the SAU was not impeded by visitors (who waited in a nearby visitors' room) and active resuscitation of patients at night did not disturb sleeping patients on the general ward.

In primary care-based health systems, it is important for GPs accurately to assess acutely ill patients and then make appropriate hospital referrals. The effectiveness of this process is unknown; however, this study supports previous work[1] in suggesting that almost 40 per cent of patients sent to hospital may be discharged immediately. An indication of how this triage system is functioning is also given by the less than adequate results of audit of referral calls and the content of the accompanying GP letter. It may be unrealistic to attempt to improve the effectiveness of GP triage, and this audit suggests that rapid assessment by an experienced surgical trainee in an SAU is an efficient way to reduce costs and improve service delivery. This is supported by the lower mean cost of £75·27 for evaluating and discharging a patient considered inappropriate for admission from the SAU (i.e. £14 226·21/189), compared with a mean cost for a 1-night hospital bed stay of £179 in a previous study[1].

Operation costs for the acute service were more accurately defined when the SAU was established. This occurred because of separation of the acute and elective services. The acute service is purchased by capitated contracts, and accurate cost estimates are beneficial as they are needed for predicted revenue and expenditure. The reduction in costs for patients seen in the SAU who do not require admission can also be passed on to those who purchase this service, and a contract similar to that for purchase of outpatient visits is being developed.

During the study period the SAU was closed after 23.00 hours for a period of 2 months due to inability to finance nursing staff. The cost of staffing the SAU for the 9-h shift between 22.00 and 07.00 hours was £129·60 (i.e. £14·40 × 9 h). This cost could be justified if only one patient was seen and discharged during the shift, as the mean cost of £75·27 is over £100 less than the cost of an overnight admission. In addition, the elective surgical service is busy with high bed occupancy and high case throughput. It is undesirable that patients be admitted unnecessarily as this may cause cancellation of elective cases[2]. These considerations suggest that it may therefore be more cost-effective to staff the SAU at night rather than close it.

This prospective audit confirms that the ready provision of an experienced surgical opinion in combination with early assessment can reduce the number of unnecessary acute admissions from GPs by 56·8 per cent (182 calls not seen plus 189 seen and sent home of 653 total calls). Significant cost savings (£10 344 over 4 months or almost £40 000 per annum) can be anticipated, with improved patient care and more effective management. This study also suggests that it is possible to reduce further the number of patients seen for assessment.

Acknowledgements

The authors thank L. Webster, L. Pearson, H. Nandha, K. English, H. Tabbak, F. Memon, D. Galvin, H. Bishop, B. Bullen, I. Haynes, S. Davis, J. Whitaker, G. Gordon, J. Makunde, A. Seaton and E. Lamuren.

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British Journal of Surgery 1996, 83, 1547

Case report

Solitary caecal diverticulum strangulated in a femoral hernia

R. M. NAUNTON-MORGAN and A. MAW

Department of Surgery, St Peter's Hospital, Chertsey, UK

Correspondence to: Mr A. Maw, Department of Academic Surgery, 4th Floor Alexandra Wing, The Royal London Hospital, London E1 1BB, UK

Hernial sacs may contain a variety of contents. This report is of an unusual case in which a solitary true caecal diverticulum was strangulated in a femoral hernia.

Case report

A previously fit 89-year-old woman presented as an emergency with a 4-day history of a lump in the right groin. Other than pain, there were no symptoms. Examination revealed a firm, tender, non-fluctuant, 7 × 4 cm, irreducible, right femoral hernia with erythema of the overlying skin. Abdominal radiographs and all other investigations were normal.

By means of a McEvedy approach, the hernial sac was explored and found to contain a necrotic, solitary, 3·5-cm long caecal diverticulum with a 1·5-cm base situated at the inferior pole of the caecum. The appendix and remainder of the caecum were normal. The diverticulum was excised, the caecal defect closed and the hernia repaired. The patient made an uneventful recovery and was discharged on the fifth postoperative day.

Discussion

Femoral hernias are commoner in women and usually contain either omentum or small bowel. They can contain the caecum, appendix, a Meckel diverticulum (Littré's hernia), testis, ovary, and even the stomach or kidney[1], but a caecal diverticulum occurring in a femoral hernia has been reported only once before, with an estimated frequency of 2 per million cases of strangulated femoral hernia[1]. This is the second case described, and bears many similarities with the first. In both, the patients were elderly women with no bowel disturbance during the course of the illness. Both patients had erythema of the overlying skin, and both hernias contained a single, isolated, completely necrotic, caecal diverticulum.

Diverticula of the caecum are infrequent in the West with a prevalence of 1–2·5 per cent in patients with colonic diverticulosis[2]. Most are false, acquired diverticula. Rarer are true, solitary, caecal diverticula. These are congenital, possibly arising as a remnant of the allantois[3], and, unlike acquired diverticula, are composed of all layers of the bowel wall[2]. They are most often situated superior to the ileocaecal valve with approximately 14 per cent located on the caecal pole[2]. Usually asymptomatic, they can become acutely inflamed and present with right iliac fossa pain, mimicking appendicitis[2]. If inflamed or necrotic at surgery, they can be treated by diverticulectomy or segmental resection. Where appearances are such that a caecal tumour cannot be excluded, hemicolectomy should be performed[2].

Although rare, if encountered, a strangulated caecal diverticulum in a hernia should be treated by resection, as in this case.

Acknowledgements

The authors thank Mr M. H. Thomas for permission to report on his patient.

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Paper accepted 18 January 1996

British Journal of Surgery 1996, 83, 1548–1552

Comparison of the cost of preventing postoperative deep vein thrombosis with either unfractionated or low molecular weight heparin

D. BERGQVIST, B. LINDGREN* and T. MATZSCH†

*Department of Surgery, University Hospital, Uppsala, *Department of Community Medicine (Malmo), Lund University and †Department of Surgery, Malmo General Hospital, Lund University, Sweden*

Correspondence to: Professor D. Bergqvist, Department of Surgery, University Hospital, S-751 85 Uppsala, Sweden

The relative costs were analysed of (1) no prophylaxis against deep vein thrombosis (DVT), (2) selective treatment of DVT after confirmation of diagnosis, (3) general prophylaxis with standard low-dose unfractionated heparin and (4) general prophylaxis with low molecular weight heparin (LMWH) in patients undergoing elective general abdominal surgery or elective hip surgery. The mean calculated costs per patient undergoing general abdominal surgery were: Swedish crowns (SEK) 1950 for no prophylaxis, SEK 5710 for selective treatment of DVT, SEK 735 for prophylaxis with unfractionated heparin and SEK 665 for prophylaxis with LMWH. The corresponding costs for hip surgery were SEK 3930, SEK 10 790, SEK 1730 and SEK 1390 respectively. Thus, the least expensive management strategy in patients undergoing elective general abdominal or hip surgery would appear to be general prophylaxis with either unfractionated heparin or LMWH. Furthermore, general prophylaxis with LMWH would appear to be more cost-effective than general prophylaxis with unfractionated heparin.

Prophylaxis against deep vein thrombosis (DVT) has gained increasing acceptance among surgeons in the past few years, but there is still some reluctance to employ this strategy[1]. The reasons for not using prophylaxis vary, but they commonly include a fear of side-effects or a concern that such a course of action is too expensive. A number of studies, however, have demonstrated that prophylaxis against DVT is cost-effective[2–16] and can reduce mortality from pulmonary embolism[17–20].

This study is a cost analysis of general prophylaxis in patients undergoing elective general abdominal surgery or elective hip surgery who are at moderate and high risk, respectively, of developing DVT. The aims of the analysis were to determine whether general prophylaxis with low-dose unfractionated heparin or low molecular weight heparin (LMWH) is more efficient than no prophylaxis or selective treatment of DVT, and whether general prophylaxis with LMWH is more efficient than general prophylaxis with low-dose unfractionated heparin.

Patients and methods

Patients

Two groups were evaluated. patients undergoing elective general abdominal surgery who were at moderate risk of developing DVT, and those undergoing elective hip surgery who were at high risk of developing DVT For both groups of patients the following four management strategies were compared: (1) no prophylaxis, (2) selective treatment of DVT following general surveillance with the fibrinogen uptake test (FUT); (3) general prophylaxis with standard low-dose unfractionated heparin and (4) general prophylaxis with LMWH.

Cost analysis

Estimations of the frequency of thromboembolism and of bleeding complications associated with general prophylaxis and the treatment of DVT used in the initial analysis are presented in *Table 1* The data in this table are based on the mean results of three reviews[17,18,21]. Basic data on the costs of the surveillance test, prophylaxis and treatment of DVT are shown in *Table 2*. The estimates of treatment costs were made on the basis of patient data from a randomized controlled trial on thromboprophylaxis[22] and financial data from Malmo University Hospital It was assumed that thromboemboli were detected clinically. Using the results of previous studies[17,18,21], it was assumed that the prophylactic effectiveness (percentage reduction in frequency of clinically detected thromboembolism compared with no prophylaxis) of unfractionated heparin was 90 per cent in general surgery and 72 per cent in hip surgery, and that the prophylactic effectiveness of LMWH was 90 per cent in general surgery and 79 per cent in hip surgery. To estimate the costs of treating a patient with pulmonary embolism, it was assumed that, of patients who had thromboembolism, 86 per cent had DVT and 14 per cent had pulmonary embolism[23]. The cost of general prophylaxis with LMWH used in the calculations was based on the mean price of the LMWHs available in Sweden (dalteparin, enoxaparin, logiparin, tinzaparin), which varied in cost by as much as 40 per cent. The doses of unfractionated heparin and LMWH used in the analysis were those recommended by the manufacturers, and the duration of prophylaxis was assumed to be 7 days after abdominal surgery and 10 days after hip surgery. It was assumed that low-dose unfractionated heparin was given twice daily and LMWH once daily, both by subcutaneous injection

Using the data presented in *Tables 1* and *2* the estimated costs of the four management strategies per patient in both general and hip surgery were calculated

Sensitivity analysis

A sensitivity analysis was performed to test the robustness of the results and conclusions. First, single variables were altered one at a time, while all others were held constant. The altered variables were as follows: prophylactic effectiveness of unfractionated heparin and LMWH; initial frequencies of thrombosis without prophylaxis; costs of treating thromboembolism; costs of treating bleeding complications resulting from prophylaxis; and prices of the various LMWHs. The break-even point was calculated for each variable This is the value at which the variable under consideration makes the management strategies under consideration equally expensive Second, the prophylactic effectiveness, initial frequencies, costs of treating thromboembolism

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Paper accepted 30 January 1996

Table 1 Data on thromboembolism and bleeding based on the mean results of three review papers[17,18,21]

	General surgery			Hip surgery		
	No prophylaxis	UFH	LMWH	No prophylaxis	UFH	LMWH
Frequency of thromboembolism						
Clinically detected	0·115	0·011	0·010	0·232	0·066	0·048
Fibrinogen uptake test	0·290	0·057	0·041	0·590	0·333	0·195
Frequency of bleeding complications						
Prophylaxis	—	0·048	0·036	—	0·048	0·036
Treatment	0·11	0·11	0·11	0·11	0·11	0·11

UFH, low-dose unfractionated heparin; LMWH, low molecular weight heparin

Table 2 Data on the costs of the surveillance test (fibrinogen uptake test), prophylaxis and treatment of deep vein thrombosis

	Mean(s.d.) (range) cost*
Fibrinogen uptake test	800
Prophylaxis	
General surgery	
UFH	140 (135–145)
LMWH	185 (165–230)
Hip surgery	
UFH	200 (190–210)
LMWH	265 (235–330)
Treatment†	
Deep vein thrombosis ($n = 13$)	7765(9580) (3865–34090)
Pulmonary embolism ($n = 2$)	65080(1125) (64280–65880)
Bleeding complications due to prophylaxis ($n = 9$)	8545(8700) (575–26085)

*Costs are expressed in SEK (Swedish crowns) and at the 1993 level of costs. When this analysis was conducted (September 1993), the Swedish crown was floating; at that time SEK100 was approximately equivalent to US $12·60 or £8·20 †Treatment costs were estimated on the basis of the resource use of 24 patients included in a randomized controlled trial[22] UFH, low-dose unfractionated heparin; LMWH, low molecular weight heparin

and costs of treating bleeding complications were either raised or lowered by 25 per cent, all at the same time.

Results

The expected costs per patient of the four management strategies under consideration in general abdominal and hip surgery are given in *Tables 3* and *4*. In both general abdominal and hip surgery, general prophylaxis was the least expensive management strategy compared with no prophylaxis or selective treatment of DVT following surveillance with the FUT. General prophylaxis with LMWH was found to be a cheaper alternative than general prophylaxis with unfractionated heparin. The cost range for general prophylaxis with LMWHs available on the Swedish market was SEK 645–710 in general abdominal surgery and SEK 1360–1455 for hip surgery. When this analysis was conducted (1993) the Swedish crown was floating; at that time SEK 100 was approximately equivalent to US $12·60 or £8·20.

Sensitivity analysis

The control group for comparison contained patients who had no prophylaxis or surveillance (group 1).

Cost of prophylaxis. In general surgery, the prophylactic effectiveness of both unfractionated heparin and LMWH was assumed to be 90 per cent. In hip surgery, it was assumed to be 72 per cent for unfractionated heparin and 79 per cent for LMWH. For the general prophylaxis strategy in general surgery to cost the same as no prophylaxis with selective treatment, the prophylactic effectiveness of unfractionated heparin and LMWH would have to be no greater than 29 and 24 per cent respectively. The corresponding values in hip surgery were 32 per cent for both unfractionated heparin and LMWH. Thus, general prophylaxis would be the regimen that cost the least, even if the prophylactic effectiveness of unfractionated heparin or LMWH were considerably lower than that initially assumed.

Initial frequency of thromboembolism. The initial frequency of clinically detected thromboembolism in the absence of prophylaxis was assumed to be 11·5 per cent in general surgery and 23·2 per cent in hip surgery. For the general prophylaxis strategy to be as expensive as the no-prophylaxis alternative, the frequency of thromboembolism in patients receiving general prophylaxis with unfractionated heparin would have to be 3·6 per cent in those undergoing general surgery and 5·0 per cent in those having hip surgery. For LMWH, the initial frequency of thromboembolism in general and hip surgery would have to be only 3·2 and 4·3 per cent respectively in order to break even. Hence, general prophylaxis is the regimen of least cost, even if the initial frequency of thromboembolism were considerably lower than assumed in the base case.

Cost of treating thromboembolism. The cost of treating thromboembolism was assumed to be SEK 16 935 on the basis of costs reported in *Table 2* and the assumption that 86 per cent of patients with thromboembolism had DVT and the remaining 14 per cent had pulmonary embolism. It was found that the cost of treating one thromboembolism could be no higher than SEK 4715 in general surgery and SEK 3125 in hip surgery for the no-prophylaxis strategy to be just as inexpensive as the general prophylaxis strategy (using LMWH). Both these figures, however, are unrealistically low at the present time.

Cost of treating bleeding complications. Using data presented in *Tables 1* and *2*, it was assumed that each bleeding complication resulting from prophylaxis cost SEK 8700. According to the sensitivity analysis, this value had to be raised by more than 400 per cent, to SEK 44 305, for the no-prophylaxis strategy to be as

Table 3 Expected cost per patient of four alternative management strategies regarding the risk of thrombosis in general surgery

	Cost per patient (SEK)				
Strategy	Surveillance test	Prophylaxis	Thromboembolism	Bleeding due to prophylaxis	Total
No prophylaxis	0	0	1950	0	1950
Selective treatment after surveillance	800	0	4910	0	5710
General prophylaxis					
UFH	0	140	185	410	735
LMWH	0	185	170	310	665

UFH, low-dose unfractionated heparin, LMWH, low molecular weight heparin

Table 4 Expected cost per patient of four alternative management strategies regarding the risk of thrombosis in hip surgery

	Cost per patient (SEK)				
Strategy	Surveillance test	Prophylaxis	Thromboembolism	Bleeding due to prophylaxis	Total
No prophylaxis	0	0	3930	0	3930
Selective treatment after surveillance	800	0	9990	0	10790
General prophylaxis					
UFH	0	200	1120	410	1730
LMWH	0	265	815	310	1390

UFH, low-dose unfractionated heparin; LMWH, low molecular weight heparin

inexpensive as the general prophylaxis strategy in general surgery (using LMWH); in hip surgery, the corresponding value would have to be SEK 79 165.

Price of low molecular weight heparin. It was found that, if the least expensive LMWH could reduce the frequency of thromboembolism in hip surgery from 23·2 to 4·8 per cent, the most expensive LMWH would have to reduce the frequency of thromboembolism by only a further 0·55 percentage points, to 4·25 per cent, to be as cost-effective. The mean price of LMWH could have been up to 37 per cent higher than that of unfractionated heparin in general surgery, and 128 per cent higher than that of unfractionated heparin in hip surgery, and general prophylaxis with LMWH would still be more cost-effective than general prophylaxis with unfractionated heparin.

Effect of altering multiple variables. The effect of altering four of the above variables at the same time by up to 25 per cent was examined. For example, in general surgery, the initial frequency of clinically detected thromboembolism was reduced from 11·5 to 8·6 per cent, the prophylactic effectiveness from 90·0 to 67·5 per cent, the costs of treating thromboembolism from SEK 16 395 to SEK 12 700, and the costs of treating haemorrhagic complications due to prophylaxis increased from SEK 8700 to SEK 10 875. Using LMWH as the prophylactic agent, the expected costs per patient in general surgery would then be SEK 1092 for the no-prophylaxis strategy and SEK 932 for the general prophylaxis alternative. Thus, the general prophylaxis strategy would still be roughly 15 per cent cheaper than no prophylaxis, despite the drastic changes in assumptions made. The results for unfractionated heparin and hip surgery were similarly stable.

Discussion

The results of this cost analysis demonstrate that general prophylaxis with either low-dose unfractionated heparin or LMWH are the least expensive strategies compared with no prophylaxis or selective treatment of DVT. This finding concurs with previous studies in which general prophylaxis has been shown to produce significant financial savings[2–16,23]. This analysis is one of the first to include patients who are at moderate risk of developing DVT.

It is of note that this cost analysis did not include determination of years of life gained through prevention of fatal pulmonary embolism. As general prophylaxis can significantly reduce the frequency of pulmonary embolism[19,23], the inclusion of costs related to its prevention would reinforce the conclusion that general prophylaxis is less expensive. In addition, although venous insufficiency after postoperative thrombosis occurs in only a small proportion of patients[24], the costs of treating this condition, which can present up to 10 years after operation, can be substantial. In a Swedish study nurses were required to dress the wounds of patients an average of 1100 times per week for every 100 000 patients with venous insufficiency[25]. The cost of personnel alone for this undertaking is SEK 500 million per year in Sweden (8·5 million inhabitants). Thus, potential savings in prevention of postoperative venous insufficiency could augment the cost savings of general prophylaxis with unfractionated heparin or LMWH.

Only one of the management strategies subjected to cost analysis included routine surveillance of the development of thromboembolism with the FUT, and this strategy proved to be the most expensive. The expected treatment costs per patient were SEK 5710 in general surgery and SEK 10 790 in hip surgery, compared with SEK 1950 and SEK 3930 when no prophylaxis was given. Had routine surveillance with the FUT been used in addition to general prophylaxis with unfractionated heparin or LMWH, the general prophylaxis strategy would probably be only slightly cheaper than the no-prophylaxis strategy. Routine surveillance for thromboembolism in patients receiving prophylaxis is rarely undertaken in clinical practice. In addition, the FUT is now used less frequently because of the potential risk of transmitting viral diseases such as hepatitis and human immunodeficiency virus. A lower cost alternative to the FUT would be to use bilateral phlebography, which detects thromboembolism with a similar frequency to the FUT. An alternative method is duplex ultrasonography, but this would probably detect fewer thromboses and the cost of the test (SEK 1200) does not make routine surveillance cost-effective.

When comparing low-dose unfractionated heparin with LMWH, the advantage of once-daily subcutaneous administration was not taken into consideration because this simpler route would not reduce the number of nurses required, and would therefore be unlikely to save money. None the less, fewer injections are advantageous for both patients and nursing staff.

There were indications that LMWH might be more effective than low-dose unfractionated heparin in reducing the frequency of proximal thrombosis, a finding supported by a number of other studies[3]. As proximal thrombosis often leads to pulmonary embolism, general prophylaxis with LMWH is potentially more cost-effective than general prophylaxis with unfractionated heparin, as it may prevent the long-term consequences associated with pulmonary embolism.

The sensitivity analysis showed that the conclusions were valid, as even drastic changes in the assumptions used in the calculations did not alter the results. It may soon be possible to treat DVT with a single daily injection of a LMWH on an outpatient basis and this may alter the outcome of the calculations by reducing hospital costs. The advantage of LMWHs in the prevention of postoperative DVT found in this analysis would then have to be re-evaluated.

The results of this cost analysis and other previously published studies and analyses[2–16,23] indicate that prophylaxis against postoperative thromboembolism can save lives and make scarce healthcare resources available for other important purposes. Although this study specifically relates to the situation in Sweden, the results of the sensitivity analysis suggest that the conclusions will be valid in other countries, and that general prophylaxis with unfractionated heparin or LMWH will remain a more cost-effective management strategy than no prophylaxis followed by selective treatment.

Acknowledgements

This work was supported by grants from the Swedish Medical Research Council (nos 00759 and 09529) and the Swedish Heart and Lung Foundation.

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Surgical workshop

Videoscopic subfascial incompetent perforator vein ablation

A. R. J. PHILLIPS and J. M. FLEISCHL
Hastings Memorial Hospital, Hastings, New Zealand
Correspondence to: Mr J. M Fleischl

Chronic venous ulceration secondary to perforator vein incompetence is a significant cause of morbidity. Surgical ablation of incompetent veins is thought to hasten healing of these ulcers[1,2]. A number of such procedures have been described which in general involve extensive dissection through compromised tissues. Such an approach can lead to wound healing problems and other complications. An endoscopic method of perforator disruption using rigid halogen lamp tubes of varying length has been reported recently[3]. A modification of the method using video laparoscopic equipment is presented.

Surgical technique

This was adapted from a technique developed by Hauer[4] and also reported in the English literature by Jugenheimer and Junginger[3] in 1992. Patients who on clinical examination are demonstrated to have incompetent lower limb perforators have ascending venography to confirm the diagnosis and identify the perforator locations. The positions of the incompetent perforators are marked on the leg before operation, using the medial or lateral malleolus as a reference point.

Operating under general anaesthetic the leg is first exsanguinated with a roller cuff; an upper thigh tourniquet is inflated to 300 mmHg. The leg is draped in a manner that allows it to be freely manoeuvred at operation. A Stortz Hassan trocar (Carl Stortz, Tüttlingen, Germany) is then introduced into the subfascial space, either medially or laterally, through a short longitudinal incision placed about the level of the tibial tubercle. Incisions are kept just posterior to the coronal plane, taking particular care to avoid injury to the common peroneal nerve when entering laterally. The subfascial space is insufflated with carbon dioxide at 20 mmHg. The 0° laparoscope (Stortz) is then advanced into the subfascial space, which is developed under direct vision by advancing and withdrawing the scope. The perforators appear in a line just anterior to the plane of the scope. A 5-mm trocar port is then introduced into the subfascial space under direct vision 3–4 cm distal to, and 2 cm anterior to, the videoscope port. Through this a hook diathermy probe is inserted; this is used for further dissection and isolation of the perforators. The perforator veins can be visualized clearly spanning the subfascial space which is maintained by the insufflated carbon dioxide. The correct position of an incompetent perforator vein is confirmed by applying pressure over the skin site marked before surgery. This can be seen videoscopically as an indentation of the subfascial space adjacent to the appropriate incompetent vein.

The perforator veins are disrupted by applying electrocautery via the hook diathermy probe. On completion, the scope and ports are removed and the skin is closed directly Soffban (Smith and Nephew, Hull, UK) and crepe bandage is applied, but not too firmly as the leg swells when the tourniquet is released. Bedrest is maintained for 24 h. Patients are then discharged home and bandages are removed at 7 days.

Discussion

This method is an improvement on that reported previously because it utilizes a single videoscope and video monitor, and uses carbon dioxide to help dissect and maintain the subfascial space thereby improving perforator visualization. All the equipment is readily available. The procedure provides a safe and effective method of accomplishing perforator disruption which avoids the wound healing problems often encountered in open procedures.

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Paper accepted 22 December 1995

British Journal of Surgery 1996, **83**, 1553

Short note

Knee-length *versus* thigh-length graduated compression stockings in the prevention of deep vein thrombosis

A. M. WILLIAMS, P. R. DAVIES,
D. I. S. SWEETNAM, G. HARPER,
R. PUSEY* and C. D. R. LIGHTOWLER*

*Departments of Orthopaedic Surgery, Royal National Orthopaedic Hospital, Stanmore and *Basildon Hospital, Basildon, UK*
Correspondence to: Mr A. M. Williams, Hillside, Exminster Hill, Exminster, Exeter EX6 8DW, UK

Graduated compression stockings can reduce the incidence of deep vein thrombosis by 60 per cent[1], by providing a decreasing compression gradient from the ankle towards the thigh. There is both theoretical and clinical evidence that compression of the thigh as well as the calf does not give extra benefit[2,3]. Although regarded as safe, improperly used stockings are not without risk. Problems are usually due to areas of localized high pressure, especially under 'rucked up' constricting bands of stocking. This is particularly so in the presence of ischaemia; manufacturers state that ischaemia is a contraindication to stocking use. Cases of arterial thrombosis have been reported[4], as well as more frequent skin necrosis, when stockings have been used in the presence of reduced arterial blood supply[5].

Patients and methods

Patients on orthopaedic wards at eight hospitals (Royal National Orthopaedic, Basildon, Orsett, Whittington, Watford General, Chase Farm, Barnet General and Southend Hospitals) were assessed To prevent prior preparation of patients by ward staff, only the authors knew of the study, arriving unannounced on each ward, wards were visited in rapid succession. The same observer visited patients within a single hospital.

If a patient wore graduated compression stockings, the following were assessed. length of stockings (knee or thigh length); size of stockings; and lower limb dimensions (measured according to the stocking manufacturer's instructions) to allow comparison of the recommended stocking size with the size actually worn. The application of stockings was assessed by the following criteria: presence or absence of constricting bands (5 mm or more in width) and of low application (more than 2 cm of unfilled stocking distal to the longest toe). To allow an overview, if the stockings were of the correct size, had no constricting bands and were positioned correctly on the limb, they were deemed 'satisfactory'.

Results

In all, 324 patients were assessed; 60 per cent were women. The median age was 67 years. Some 131 patients (40 per cent) wore stockings and of these 79 (60 per cent) wore thigh-length stockings, either T.E.D. (The Kendall Company, Basingstoke, UK) or Brevet TX (Brevet Hospital Products, Whitchurch, UK), and 52 (40 per cent) wore knee-length stockings, all Brevet TX. The results are summarized in *Table 1*.

Table 1 Application of graduated compression stockings

	Length of stocking	
	Thigh length (%)	Knee length (%)
No. assessed	79 (60)	52 (40)
No. of legs with stocking of correct size	42 (53)	29 (56)
No. of stockings producing constriction bands	44 (56)	7 (13)
No of stockings positioned too low	30 (38)	1 (2)
No. of stockings satisfactory overall	10 (13)	26 (50)

Values in parentheses are percentages

Discussion

The widespread failure to use stockings properly suggests a complacency in practice which might cause local complications and prevent adequate prophylaxis. It is essential for those using graduated compression stockings to understand the importance of correct application and sizing of stockings, and the risks of poor fitting. Questioning of patients who had worn both lengths of stocking revealed that they found knee-length ones more tolerable and that they often rolled thigh-length ones down. This, and the fact that they are easier to put on, probably accounts for a much higher rate of 'satisfactory' stockings in the knee-length group. In addition, knee-length stockings are cheaper by approximately £2·00 per pair, according to prices paid by one of the hospitals studied in December 1995.

The authors recommend that the use of knee-length stockings should replace that of thigh-length garments on the grounds that the former are equally efficacious, more likely to be fitted correctly, and are cheaper.

Paper accepted 27 January 1996

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British Journal of Surgery 1996, 83, 1554–1557

Pedal bypass for limb-threatening ischaemia: an 11-year review

H.-H. ECKSTEIN, H. SCHUMACHER, N. MAEDER, S. POST, Th. HUPP and J.-R. ALLENBERG

Department of Surgery, Vascular Surgery Section, Ruprecht-Karls University of Heidelberg, Im Neuenheimer Feld 110, D-69 120 Heidelberg, Germany

Correspondence to: Dr H.-H. Eckstein

Fifty-six patients with limb-threatening ischaemia had pedal revascularization with either autologous vein ($n = 39$) or sequential composite graft with a 6-mm polytetrafluoroethylene prosthesis and autologous vein ($n = 17$); 75 per cent had gangrene and skin necrosis and 25 per cent had ischaemic rest pain alone. Twelve grafts occluded within the first week, and resulted in major amputation in eight patients after unsuccessful revision. Two patients required amputation for persistent ischaemia despite a patent bypass. One patient died from bowel perforation (2 per cent). In 47 (84 per cent) of the 56 patients limb and life were preserved. The primary patency rate after 1, 2 and 4 years was 65, 55 and 55 per cent respectively, the secondary patency rate was 71, 62 and 62 per cent, and cumulative limb salvage rates were 77, 71 and 66 per cent. Life-table survival rates during follow-up (median 25 (range 0–112) months) were 89, 78 and 52 per cent respectively after 1, 2 and 4 years. Thirteen of 21 patients who died during follow-up did not require major amputation. Pedal reconstruction with autologous vein provides limb salvage until death in nearly two-thirds of patients with critical limb ischaemia resulting from crural arterial occlusive disease.

The incidence of critical limb ischaemia is estimated to be 500–1000 patients per million in western Europe. Some 25 per cent of these patients are treated conservatively or by percutaneous transluminal angioplasty, 25 per cent have a primary amputation and 50 per cent receive arterial reconstruction[1–3]. In particular, patients with infrapopliteal arterial occlusive disease at preoperative diagnostic angiography are frequently considered unsuitable for reconstruction. The perioperative mortality rate after major amputation is about 10 per cent and the prognosis is poor in patients who cannot walk with a prosthesis or who are confined to bed or wheelchair[4]. In the past decade the limit of distal revascularization has been extended to the arteries of the ankle and the foot, and long-term patency and limb salvage rates between 60 and 90 per cent have been recorded even in diabetic and multimorbid patients[5–20]. Femorodistal revascularization down to the foot vessels may reduce the number of major lower limb amputations by 25–50 per cent[12,21–23]. These results have, however, been achieved in few hospitals and await validation in nationwide or large studies.

To update data[24] and to re-evaluate the criteria for pedal bypass grafting, all patients who had arterial reconstruction with vein to the pedal vessels for limb-threatening ischaemia between April 1984 and July 1995 were reviewed retrospectively.

Patients and methods

Some 56 consecutive pedal vein bypasses were performed in 38 men and 18 women of median age 67 (range 34–88) years. Forty patients (71 per cent) had diabetes mellitus, 37 suffered from hypertension and 27 had coronary heart disease, with previous myocardial infarction in 11. Thirty-four patients were cigarette smokers and 15 had had a previous arterial reconstruction: thromboendarterectomy of the femoral artery (three), femoropopliteal bypass (six) and femorocrural bypass (six). Three patients had a contralateral major amputation. Five patients with entirely prosthetic grafts from the early 1980s and six who had had exploration but no suitable vessels for bypass were excluded from the study. All pedal reconstructions were done for limb salvage. The indication for pedal reconstruction was ischaemic rest pain alone in 14 patients (25 per cent) which included four with acute ischaemia due to arterial thrombosis (thrombolytic therapy was not available). The remainder (75 per cent) had tissue loss as a result of gangrene or non-healing ulcers.

Preoperative evaluation included history and physical examination, Doppler ultrasonography, foot radiography and bacterial culture of areas of skin necrosis. Patients with infected gangrene or ulcers received a broad-spectrum antibiotic as appropriate.

All patients had transfemoral angiography but, in addition, a selective arteriogram of the foot was taken with radiographs in anteroposterior and lateral positions by selective contrast injection into the common femoral artery if no distal vessel was otherwise detected. Patients with aortoiliac disease or a patent popliteal or crural artery for femorodistal bypass were not considered candidates for pedal bypass. Primary amputation was considered only when no distal vessel could be detected with Doppler ultrasonography or angiography, or if the patient was multimorbid and confined to bed for other reasons.

The operative procedures and site of the distal anastomosis are shown in *Table 1*. The site of proximal anastomosis was based on preoperative angiography, whereas the level of the distal anastomosis was determined during operation after exposing the artery. Criteria for proceeding with the bypass were a smooth injection of heparin–saline solution in the distal outflow and a distal vessel diameter of at least 2–3 mm. Calcification in the artery was not a contraindication, although it rendered the procedure more difficult In 38 patients (68 per cent) the distal anastomosis was to the dorsal pedis artery and in 18 (32 per cent) to the posterior tibial artery below the ankle using an end-to-end anastomosis in 38 cases and an end-to-side anastomosis in 18. All distal anastomoses were performed under loupe magnification. When possible, autologous vein was used from the same limb ($n = 39$) with the proximal anastomosis above knee level in 18 cases. The proximal anastomosis was performed below the knee when there was adequate inflow to the popliteal or a crural artery ($n = 21$). When the length of saphenous vein was inadequate, a composite ('jump') graft was done, first with a segment of 6-mm polytetrafluoroethylene (PTFE) to the popliteal artery and then a segment of reversed saphenous vein

Paper accepted 17 January 1996

Table 1 Operative procedure, site of anastomosis and type of pedal graft in patients

		Distal anastomosis		
	No. of patients	Dorsal pedis artery ($n=35$)	Posterior tibial artery ($n=19$)	Medial plantar artery ($n=2$)
Long vein (above knee)	18	9	8	1
Proximal femoral artery	10			
Distal femoral artery	8			
Short vein (below knee)	21	12	8	1
Popliteal artery	15			
Crural artery	6			
Composite 'jump' graft	17	14	3	0

Saphenous vein used as reversed graft in 26 patients, non-reversed bypass in seven and *in situ* bypass in six

was taken from the distal part of the PTFE graft to a pedal artery ($n=17$) To assess the adequacy of the distal anastomosis and to look for residual arteriovenous fistulas after *in situ* bypass, completion on-table angiography was performed in 15 patients (routinely since 1993). Concomitant toe amputation was done in five cases Intraoperative systemic heparinization was routine; patients were anticoagulated with warfarin after operation

Follow-up was obtained from outpatient records and telephone interviews Five patients were lost to follow-up after 17–65 months. Follow-up angiography was required only if graft failure was suspected. Patient survival, graft patency and limb salvage rates were calculated according to the Kaplan–Meier method with log rank testing[25,26]. $P<0.05$ was considered statistically significant.

Results

Early results

One perioperative death occurred secondary to a bowel perforation. Twelve grafts (21 per cent) occluded within the first week but only three graft revisions (thrombectomy, local lysis and correction of the distal anastomosis) were successful. In two cases major amputation was postponed by conservative treatment whereas two other patients required amputation for persistent ischaemia in spite of a patent bypass. Altogether, early major amputation was necessary in eight (14 per cent) of 56 patients. Forty-seven (84 per cent) of the patients were discharged home with a functioning graft and intact limb.

Wound infection (incisions, vein harvesting area) was observed in three patients and treated conservatively. No graft infection occurred and no graft was lost because of wound infection. Median hospital stay was 23 days. After discharge, wound care was performed in the outpatient department or at another hospital (15 patients were transferred to another hospital with a rehabilitation ward or for treatment of other medical conditions).

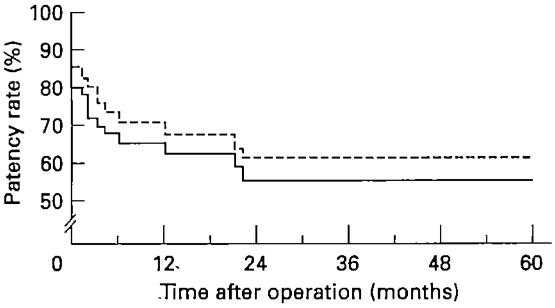
Late results

The primary patency rate after 1, 2 and 4 years was 65, 55 and 55 per cent respectively; the secondary patency rate was 71, 62 and 62 per cent (*Fig. 1*). There were three successful graft revisions after early bypass occlusion and one successful revision after late occlusion. The latter occurred after 4 months because of excessive hyperplasia occluding the distal anastomosis, and was revised by thrombectomy and vein patch. In this series there was no difference in patency between short autologous (proximal anastomosis below the knee) and long (proximal anastomosis above the knee) vein grafts: the former resulted in a secondary patency rate of 82 and 73 per cent after 1 and 2 years respectively, whereas long venous grafts achieved rates of 94 and 74 per cent respectively. Results for composite grafts were worse, with secondary patency rates of 52 and 44 per cent after 1 and 2 years respectively (*Fig. 2*). The difference in patency between all vein bypasses ($n=39$) and the composite jump grafts ($n=17$) was statistically significant ($P<0.05$, log rank test).

Sixteen patients required above-knee amputations; eight were performed early and eight during follow-up (median 4 (range 2–47) months). Cumulative limb salvage rates were 77, 71 and 66 per cent after 1, 2 and 4 years respectively (*Fig. 3*).

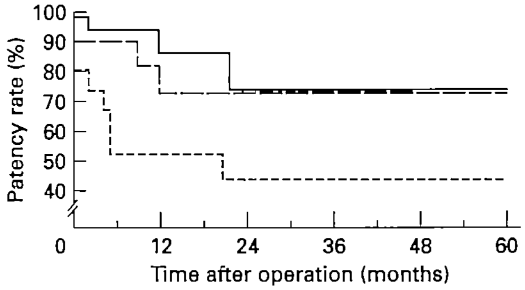
Survival

Life-table survival rates during follow-up (median 25 (range 0–112) months) were 89, 78 and 52 per cent after 1, 2 and 4 years respectively (*Fig. 3*). The overall mortality



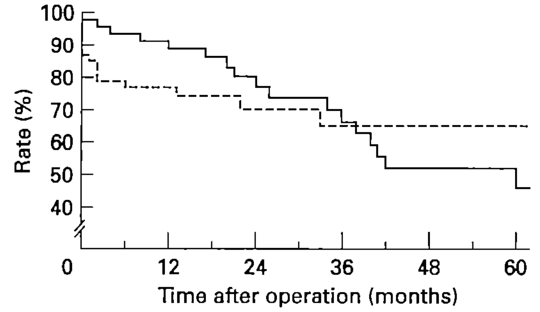
No. at risk						
Primary	56	26	14	10	6	4
Secondary	56	26	14	10	6	4

Fig. 1 Kaplan–Meier curves of primary (——) and secondary (– – –) patency rates in 56 pedal vein bypasses



No at risk						
Femoropedal	18	12	5	3	2	2
Popliteopedal	21	9	6	5	5	3
'Jump' grafts	17	7	5	3	2	2

Fig. 2 Kaplan–Meier curves of secondary patency in 56 pedal vein bypasses: ——, femoropedal long vein; – – –, popliteopedal short vein (below knee; includes cruropedal bypasses); ----, composite polytetrafluoroethylene and vein 'jump' graft. $P<0.05$ ('jump' graft *versus* femoropedal and popliteopedal bypass, log rank test)



No. at risk						
Survival	56	38	26	19	13	9
Limb salvage	56	30	18	14	8	5

Fig. 3 Kaplan–Meier curves of limb salvage (– – –) and survival (——) in 56 patients undergoing pedal vein bypass

rate was 21 (38 per cent) of 56 patients (cardiac disease, 13; stroke, four; bronchial cancer, two; acute limb ischaemia following graft occlusion, one; perioperative death, one; median survival 34 months). Of these 21 patients, 13 died without needing major amputation.

In the subgroup of patients initially treated successfully, 18 of 47 died (median survival 36 months). In addition to those who died following graft occlusion, four patients needed above-knee amputation following graft occlusion. In conclusion, 13 of 18 patients who died, who initially had a patent bypass at discharge, did not need amputation before death (median survival 21 (range 2–82) months).

Discussion

Primary amputation is offered as an alternative to many patients with limb-threatening ischaemia and a distal pattern of peripheral arterial occlusive disease for the following reasons: advanced age, multiple risk factors, increased cost and prolonged hospitalization, increased morbidity after failed revascularization and general pessimism about inframalleolar reconstructions. Several specialized centres have reported long-term patency and limb salvage rates of up to 90 per cent in bypass grafting to the distal arteries beyond and below the ankle[5–20,27,28].

Pedal vein bypass has represented 8 per cent of distal revascularizations carried out in this institution since 1984. There was a high proportion (71 per cent) of diabetics in this patient population, who typically have a distal pattern of arteriosclerosis with occlusion of infrapopliteal arteries but sparing of the foot vessels[8,17,18,28–30]. In a post-mortem study of 140 legs amputated for severe ischaemia, 65–70 per cent of the paramalleolar and foot vessels were patent, in contrast to the proximal infrapopliteal vessels which were occluded in nearly 90 per cent of cases[31]. Selective angiography with injection of contrast into the femoral artery is, in combination with Doppler ultrasonography, a prerequisite to pedal reconstruction. This was confirmed by Pomposelli *et al.*[28] in a series of 384 dorsalis pedis bypasses in which the chances of a successful bypass were 99 per cent when a dorsal pedal artery was visualized on the preoperative arteriogram but only 57 per cent when no artery was seen but an audible Doppler signal was present.

In the present study 47 (84 per cent) of 56 patients who had pedal arterial reconstruction were discharged or transferred to another hospital with a patent bypass. The operative mortality rate of 2 per cent corresponds with other results reported in the literature (0–9 per cent) and compares well with survival rates after major amputation, which has an operative mortality rate of 7–15 per cent[3–6,8,17–20]. In other series the rate of early graft failure ranged from 5 to 10 per cent, with a 50 per cent chance of successful revision[8,15,28,30]. This is lower than the early graft thrombosis rate of 21 per cent during the first 30 days in the present study. In two patients persistent ischaemia and spreading foot sepsis resulted in major amputation, despite a patent bypass, as also reported by others[5,6,10,19,20].

Autologous vein is the graft material of choice for pedal bypasses. In large series no significant difference was found between translocated grafts (reversed:non-reversed) and *in situ* grafts[8,28]. The subgroups in this study were too small for comparison.

Graft patency rates in this series are comparable with most reports made during the past decade with 2-year cumulative patency rates between 59 and 81 per cent[9,20,30]. Better results may be achieved in diabetics; 5-year primary and secondary patency rates of 68 and 82 per cent respectively have been described[15,28]. Gloviczki *et al.*[30] found a statistically significant difference between 67 diabetic and 33 non-diabetic patients, with 3-year patency rates of 74 and 50 per cent respectively in favour of the diabetics. Diabetic patients with ischaemic foot lesions are often good candidates for pedal bypass and should not be rejected from preoperative evaluation. Forefoot infections sometimes persist in diabetics, especially when the plantar arch is incomplete, which may be the reason for limb loss even if the bypass is still patent[19,20].

The small difference between primary and secondary patency rates, with only one successful late revision, reflects the fact that the pedal arteries are the most distal level for revascularization. Early revisions can be successful only in cases of technical error. A duplex surveillance programme might detect correctable graft stenosis before graft thrombosis and improve long-term results[28].

In this small study the inflow site did not affect graft patency. In spite of similar findings by Schneider *et al.*[8] in 256 tibial and pedal bypasses, use of the most distal inflow site (distal superficial femoral, popliteal or even a crural artery) is preferable provided there is no proximal arterial stenosis. A short bypass facilitates the operation in terms of obtaining suitable vein and reduces the length of incisions[7–10,17,19].

If there was no available vein for a long graft, a composite 'jump' graft (6-mm PTFE to the popliteal artery with vein to the ankle) was used. As others have found[32], long-term patency was significantly worse compared with all vein bypasses. Composite grafts to pedal vessels appear to have patency and limb salvage rates comparable with those of PTFE femoropopliteal grafts[33]. However, the results of PTFE-only grafts to pedal arteries are poor and they should be avoided.

In this patient population the cumulative limb salvage rate was 77, 71 and 66 per cent after 1, 2 and 4 years respectively which, according to recent data, is about 7 per cent higher than the corresponding patency rates[5,8,13,20,34]. Not every graft occlusion causes a new limb-threatening emergency because tissue lesions have healed while the bypass was patent with development of collateral vessels. In addition it has to be recognized that the definition of 'critical limb ischaemia' does not mean that major amputation must be performed in every case, as conservative therapy is occasionally successful[35].

As with other series, these patients with critical limb ischaemia had a limited life expectancy[8,28,36]: only 52 per cent survived 4 years; 21 of 56 patients died during follow-up. Bearing in mind the limited possibility of achieving rehabilitation and mobility with an artificial limb after amputation, especially in the elderly multimorbid patient, limb salvage in two-thirds of patients until death seems to be the most important result of this study.

The present results suggest that pedal vein bypass provides limb salvage in two-thirds of patients with limb-threatening crural arterial occlusive disease. In these cases selective angiography is necessary, even in the presence of a popliteal pulse, when revascularization of pedal arteries is considered. Primary major amputation should be performed only in patients who are confined to bed or who have severe foot infection and no patent distal vessels detected by angiography or Doppler ultrasonography.

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British Journal of Surgery 1996, 83, 1558

Surgical workshop

Rectus sheath bupivacaine analgesia after aortic surgery

P. CURLEY, A. GRAINGER, G. C. LAST and J. M. D. GALLOWAY

Department of Vascular Surgery, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, UK

Correspondence to: Mr P. Curley

Effective postoperative analgesia may reduce surgical morbidity after aortic surgery[1]. The use of epidural opioid or local anaesthetic infusions has recently been reviewed[2,3]. While there is some early evidence of reduced morbidity, mortality and hospital costs[4] with the use of epidurals, they may be associated with respiratory depression and hypoxaemia[5]. Patient-controlled intravenous analgesia is associated with greater hypoxaemia than epidural analgesia[5]. Infusion of bupivacaine for nerve sheath block after amputation reduces postoperative opioid requirements[6]. A simple technique for the infusion of bupivacaine into the lateral rectus sheath for postoperative analgesia in transverse upper abdominal surgery is described.

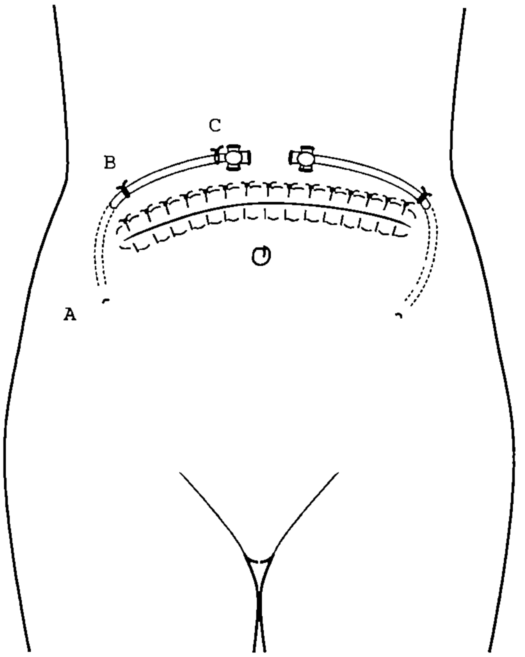

Fig. 1 System used for bupivacaine infusion after aortic surgery. Redivac needle insertion (A) in a Cephalad direction. The needle enters between the fascial layers of the rectus sheath at this point and exits both the sheath and skin at point (B). The needle is cut off at point (C) and a 16-G Venflon is inserted into the cut end of the drain tubing (C). The drain tubing and Venflon are sutured to skin

Paper accepted 13 January 1996

Surgical technique

After transverse upper abdominal incision for aortic aneurysm repair, the rectus sheath is closed in two layers with 1 polydioxanone (PDS; Ethicon, Edinburgh, UK). Before the lateral aspect of the anterior sheath is closed, a Redivac (Biomet, Bridgend, UK) drain tube is placed bilaterally. The needle is inserted just lateral to and approximately 5 cm below the level of the incision, pointing cranially. The needle and its trailing drainage tube are directed into the sheath and brought out through the skin approximately 6–7 cm above the wound. The tube is drawn in the direction of the needle so that all of its length lies beneath the skin at the lower insertion point. In this position the drainage holes of the tube all lie within the rectus sheath lateral to the incision in the plane of the abdominal wall nerves.

The needles are then removed and the tubing above the wound trimmed to approximately 8 cm in length. A 16-G Venflon (Vygon, Cirencester, UK) is then introduced into the upper end of the drainage tube, the trocar is removed and the flange sutured to skin (*Fig 1*). Through each port 10–20 ml 0·5 per cent bupivacaine is introduced at the end of the operation and repeated every 6 h for the first 3–4 days until the patient is mobile.

Discussion

Over 150 patients have been treated with this approach. No wound complications referrable to the technique have been identified.

While epidural infusions are undoubtedly useful, both for postoperative pain relief and to aid haemodynamic control during operation, they are not without complications including epidural abscess[7], paraplegia, urinary retention and nausea[3]. The technically simple procedure of bupivacaine infusion into the rectus sheath may be a useful adjunct in major abdominal surgery through a transverse incision but requires formal comparison with epidural analgesia.

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British Journal of Surgery 1996, 83, 1559–1562

Prospective randomized trial comparing sequential avulsion with stripping of the long saphenous vein

B. KHAN, S. KHAN, M. G. GREANEY and S. D. BLAIR

Clatterbridge Hospital, Bebington, Wirral, Merseyside L63 4JY, UK
Correspondence to Mr S. D Blair

Eighty patients with primary varicose veins of the long saphenous system were randomized to have the long saphenous vein removed either by stripping to below the knee or by sequential avulsion. There was no difference between the two methods in the time taken to remove the vein. There was significantly more pain after stripping during the week following operation ($P < 0{\cdot}001$). Median pain score after stripping was 5, reducing to 3 at 1 week, compared with 2, reducing to 1, for sequential avulsion. Median area of bruising measured at 1 week was 160 (range 0–1800) cm^2 for stripping and 56 (range 0–544) cm^2 for sequential avulsion ($P < 0{\cdot}01$). Sequential avulsion is less painful, reduces bruising and avoids a significant scar below the knee.

Evidence has accumulated that removal of the long saphenous vein (LSV) from the groin to below the knee is important in reducing recurrence of varicose veins[1–3]. Traditionally this has been done with a vein stripper and olive. However, it has been observed that the use of a vein stripper is the main cause of pain and bruising after operation. These problems reduce mobility and prolong the return to full normal activity. In addition, a significant scar is left below the knee where the olive passes through the skin, compromising the cosmetic benefit. To overcome these defects, sequential avulsion of the LSV has been developed. There has never, so far, been a prospective randomized trial comparing the two methods.

Patients and methods

Eighty patients, presenting over a 9-month period with primary varicose veins without short saphenous incompetence on Doppler ultrasonographic assessment, were randomized on alternate weeks to have the LSV removed from the thigh either by stripping or by sequential avulsion. All aspects of the procedure were standardized, including analgesia. This consisted of piroxicam melt before operation, local infiltration of groin wounds with 10 ml bupivacaine 0·5 per cent at operation, and ibuprofen 200 mg once daily for the first 4 days after surgery. To reduce haematoma, all patients were bandaged at the end of the procedure with Panelast acryl bandages (Vernon-Carus, Penwortham Mills, Preston, UK) from metatarsal heads to upper thigh. This short-stretch adhesive bandage was left in place for 1 week[4].

As part of the informed consent for the trial, the same information sheet was given to all patients. This explained the rationale for the trial and gave standard postoperative instructions irrespective of the procedure carried out. All patients went home within 24 h of the procedure; some older patients who had their operation late in the day stayed overnight. Patients were unaware of which operation had taken place until after the bandages were removed.

Operations

Stripping. Following standard saphenofemoral flush ligation of the LSV, it was exposed just below the knee and a stripper wire passed either from below or above. A medium olive was put on the lower end and pulled proximally to lie just above the lower wound which was then closed with subcuticular polyglactin. Multiple avulsions of varicosities were then carried out, and finally the stripper was withdrawn from the groin as the Panelast acryl bandages were applied.

Sequential avulsion. Following standard saphenofemoral flush ligation of the LSV the vein was pulled taut in a cephalad direction. A forefinger was pushed down into the thigh posterior to the vein via the groin wound and a simple stab made just distal to the finger The upper portion of the vein was then directed on to a hook or clip and delivered through the stab incision (*Fig. 1*). The LSV was again put on traction to render it taut in the thigh; it could be palpated about 10 cm distally. A further stab incision was made at this point and the upper portion of vein hooked out. This procedure was repeated sequentially down the thigh until the whole LSV was removed (*Fig 2*). Local pressure was applied to the groin wound. Multiple avulsions of varicosities were then carried out as necessary and a Panelast acryl bandage applied.

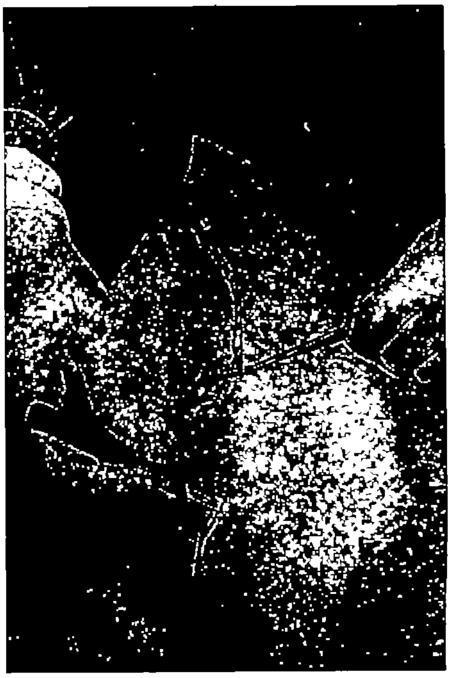

Fig. 1 Sequential avulsion in the thigh. The vein is pulled taut such that it bow strings and a stab incision is made over the vein distally where it can be palpated

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Presented to the Vascular Society in Edinburgh, November 1994
Paper accepted 22 December 1995

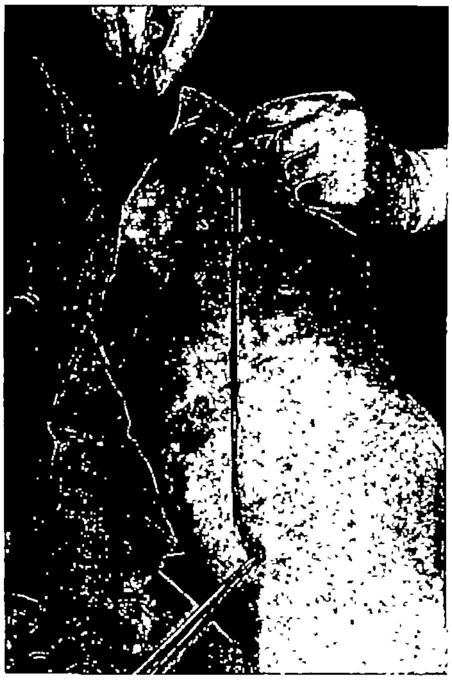

Fig. 2 Sequential avulsion. The whole long saphenous vein is brought out intact

Surgeons recorded the number of avulsion sites needed to remove the LSV, and the number of additional avulsion sites to remove varicosities. The time to remove the whole LSV was recorded, and whether removal was complete. For the purpose of this trial all avulsions in both groups were carried out using microhalsted clips. The operations were evenly distributed between the four authors.

Postoperative assessment

Patients filled in a postoperative symptom chart which included a daily linear analogue pain score ranging from 0 to 10 and a daily activity score ranging from 0 to 7 (*Table 1*). They returned to the ward after 1 week to have their bandages removed. The symptom chart was collected and wounds assessed for complications of haematoma or infection by one of two registrars The area of bruising in the thigh was measured in two dimensions. A further assessment was made at 6 weeks to enquire about any late complications Patients were specifically asked when they returned to work or full normal activity.

Table 1 Activity scores

1 Unable to walk around
2 Can walk if absolutely necessary
3 Can walk around house, but not up stairs
4 Mobile around house including stairs
5 Mobile outside with difficulty
6 Freely mobile outside
7 Back to full normal activities including work

Statistical analysis

ARCUS-ProStat statistical package (Iain Buchan, Arrowe Park Hospital, Liverpool, UK) was used to analyse data Non-parametric tests were used to compare groups (Mann–Whitney *U* test). A Wei-Lachin statistic was used to analyse the difference between groups on a daily basis. In addition the χ^2 test with Yates' correction for continuity was used.

Results

Eighty patients were entered into the trial, 40 in each group. There were 25 men and 55 women of median age 47 (range 22–69) years. There was no significant age or sex difference between the two groups.

Median (range) time to remove the LSV from the thigh was the same for both methods, 6·5 (4–9) min. However, in five patients randomized to stripping, the wire could not be passed either from above or from below because of tortuosity of the vein. In two patients randomized to sequential avulsion a complete length of long saphenous vein was not removed as the vein snapped under tension.

Median (range) number of avulsion sites in the thigh for sequential avulsion of the LSV was 5 (4–7). The median number of avulsions of varicosities in the calf was 9 for stripping and 10 for avulsions. There was no correlation between the number of avulsions in the calf and pain after operation.

Significantly more pain was experienced by those undergoing stripping than sequential avulsion during the whole week ($P<0{\cdot}001$). On the day of operation median pain score was 5 for stripping and 2 for sequential avulsion. The proportion of patients experiencing no pain on the day of operation was 12 of 40 for sequential avulsion and four of 40 for stripping. During the first week after operation pain gradually subsided in both groups. Median pain score at 1 week was 3 for stripping and 1 for sequential avulsion (*Fig. 3*).

Analysis of activity scores showed that on the day of discharge 13 of 40 patients who had undergone stripping could not climb stairs; six of 40 patients who had undergone sequential avulsion were limited in this way. Over the whole week there was no significant difference in activity. By the end of the week 70 per cent were fully mobile outdoors. Forty-seven of 62 (76 per cent) of those in employment returned to work within 2 weeks (*Fig. 4*).

Three patients had minor sensory loss in the saphenous nerve distribution. Two of these underwent stripping. At 1 week, measurement of bruising demonstrated that the bruised area ranged from 0 to 1800 (median 160) cm^2 for stripping and from 0 to 544 (median 56) cm^2 for sequential avulsion ($P<0{\cdot}01$).

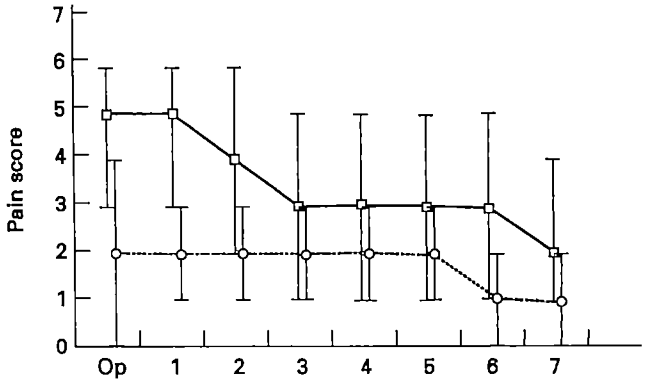

Fig. 3 Median (interquartile range) pain scores after operation. Stripping (□) was significantly more painful than sequential avulsion (○) ($P<0{\cdot}001$, Wei-Lachin statistic)

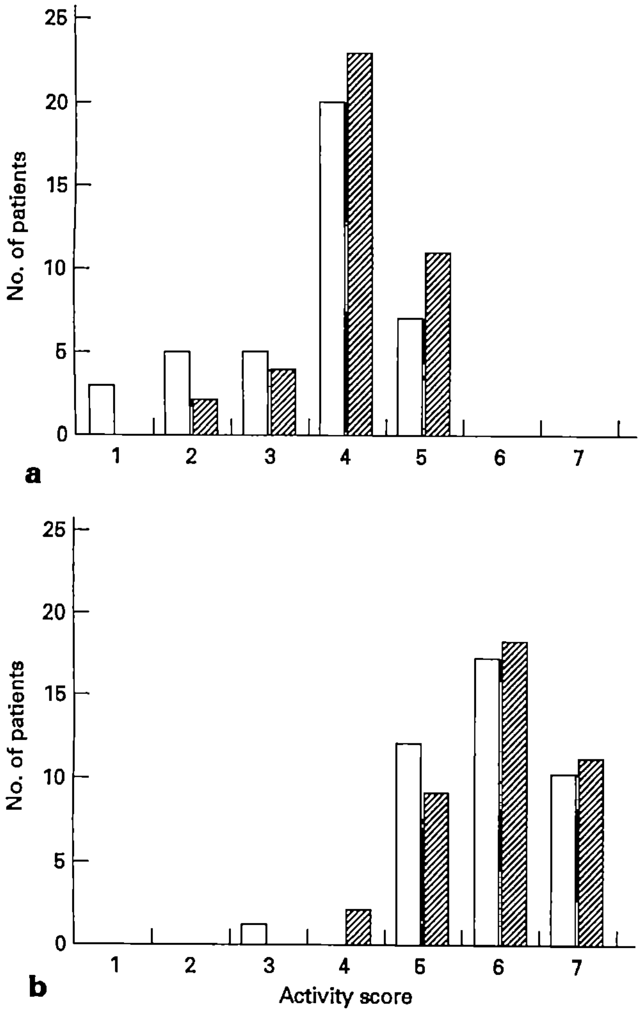

Fig. 4 Activity scores on a the first and b the seventh day after operation in patients who had stripping (□) or sequential avulsion (▨)

Discussion

The importance of removing the LSV to prevent recurrence of varices has been clearly shown. Sarin *et al.*[2] collected the results of seven controlled trials comparing saphenofemoral ligation with and without stripping. When the LSV was stripped the mean recurrence rate was 18·7 per cent compared with 35·1 per cent without stripping. This is explained by the finding that, if the LSV is not removed, on subsequent duplex scanning there is retrograde flow in 45 per cent of residual LSVs[1,2]. In addition to removal of the LSV, recurrence is reduced by good preoperative assessment of the sites of incompetence and appropriate surgical attention to the saphenofemoral junction site[3].

Much of this was appreciated 20 years ago when Rivlin[5] reported a 7 per cent rate of recurrence at 10 years. Despite this, many surgeons still do not remove the LSV routinely. Perhaps the reasoning behind this is the perceived morbidity associated with stripping. This consists of pain, bruising and a scar below the knee which may be unsightly and troublesome.

To overcome the unsightly scar below the knee several ingenious methods have been described. In cryostripping the vein is frozen and then snapped below the knee before being drawn upwards. With pin-stripping a rigid wire is directed down the vein and up to the skin below the knee, where a stab incision is made to deliver the wire stripper. Avoiding an olive on the end of the wire, the vein is tied to the stripper and inverted into itself[6–8]. However, none of these techniques addresses the problem of pain produced by stripping the vein out with one continuous movement and their effects have not been studied in prospective randomized trials.

The present study bears out the perceived morbidity of stripping as far as pain and bruising are concerned. It was surprising that 13 of 40 patients who had had stripping were unable to climb stairs at home on discharge. This has a bearing on the suitability of the procedure for day-case surgery. In contrast, 12 of 40 undergoing sequential avulsion had no pain on the day of operation; the same analgesia was used for all patients. With any method of removing varicose veins, postoperative bleeding and pain can be significantly reduced by high-compression adhesive bandages instead of crepe[4].

It has been shown that removing the LSV by sequential avulsion avoids not only the scar below the knee but also much of the pain and bruising. Perhaps the reason for this is that avulsing a segment of LSV requires very little force, rendering the procedure less traumatic than stripping. In addition, during avulsion side branches or a double LSV can be avulsed separately to a point some distance from the main track of the LSV itself. This may result in less bleeding, as the side branches go into spasm some distance away from the main track.

Long-term patient satisfaction with the outcome of stripping has been shown to be better than that for saphenofemoral ligation and avulsion[9]. In this study the LSV was removed from the thigh by both methods, in anticipation that all patients would have a satisfactory long-term outcome (from their own perspective) with a reduced chance of recurrence. It was surprising how different the patients' perceptions of the operations were, despite standardization of all variables. Great efforts had been made to prevent patients knowing which operation they had undergone (until it became clear 1 week after surgery). They knew that they were being randomized, but did not know that all patients being treated on any week were having the same procedure; any comparison of symptoms by patients would not have biased the result. As the pain and activity score sheets were collected 1 week after surgery, there was inadequate time for patients to have forgotten how painful or debilitating the procedure had been, and all score sheets were collected before bandages were removed to reveal the nature of the operation. Sequential avulsion was significantly less painful, caused less bruising and left no significant scar below the knee.

As sequential avulsion is reliable in removing the whole LSV without the expense of a stripper and without complication or increase in operating time, the authors advocate this as a standard method for treating primary varicose veins of the long saphenous system.

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Editors' announcement

Structured abstracts

The Journal has watched with interest developments in the presentation of abstracts in scientific journals. We have seen some journals adopt abstracts with 12 or more subheadings, each supported by a few words. In the defence of good readable prose, we resisted moves towards that style. However, we are aware that breaking up an abstract into several paragraphs may improve its readability and enable the reader to grasp the content more effectively. Four paragraphs suffice, corresponding to the introduction, methods, results and discussion sections of the paper in order to accommodate this extra information. The Editors recognize that a larger word limit than the present 150 words will be necessary.

With effect from the January 1997 issue, all abstracts will be printed in the following format: they will be no more than 200 words long, written in clear prose, and presented in four paragraphs.

Background. This should state why the study was done and its main aim.

Method. This should describe the patients, laboratory material and other methods used.

Results. The main findings of the study should be stated briefly, including important numerical values.

Conclusion. The main conclusion drawn from the results should be stated. Controversial or unexpected observations may be highlighted but this section should be brief.

Authors whose papers have already been accepted and are scheduled for publication in 1997 will be asked to revise the abstract in accordance with these guidelines. Instructions for Authors have been revised and all new submissions to the Journal should take account of these revised instructions. Please note that only original articles and reviews require an abstract.

R. C. N. Williamson
J. A. Murie
C. D. Johnson
J. J. Earnshaw
P. J. Guillou

British Journal of Surgery 1996, 83, 1563–1566

Prospective randomized trial comparing postoperative pain and return to physical activity after transabdominal preperitoneal, total preperitoneal or Shouldice technique for inguinal hernia repair

P. SCHRENK, R. WOISETSCHLÄGER, R. RIEGER and W. WAYAND

Second Department of Surgery and Ludwig Boltzmann Institute for Surgical Laparoscopy, AKH Linz, Linz, Austria
Correspondence to: Dr P. Schrenk, Second Surgical Department, Allgemein Offentliches Krankenhaus Linz, Krankenhausstrasse 9, A-4020 Linz, Austria

In a prospective randomized study postoperative pain, analgesic consumption, return to physical activity and work, cosmetic result and experience with the type of operation were assessed in 86 patients undergoing inguinal hernia repair by means of either the Shouldice technique ($n = 34$), the laparoscopic transabdominal preperitoneal (TAPP) ($n = 28$) or total preperitoneal (TPP) ($n = 24$) repair. Patients having TAPP repair had decreased visual analogue scale scores for pain on the day of operation compared with those undergoing TPP and Shouldice repair (4·8 *versus* 6·5 and 6·2 respectively, $P = 0{\cdot}02$) and on the first postoperative day compared with TPP (4·0 *versus* 6·0, $P = 0{\cdot}01$). There was no difference between the three groups for days 2, 3, 4, 5 and 30 after operation. Patient satisfaction with the operation, analgesic consumption, return to physical activity such as walking, driving, climbing stairs, running, bicycling and sexual intercourse, as well as return to work, was comparable in the three groups. There was a better cosmetic result after TAPP and TPP repair. This study failed to demonstrate significant benefits from laparoscopic hernia repair over the Shouldice technique.

New techniques for inguinal hernia repair with a video-endoscopic approach have gained increased popularity among patients and surgeons as they may be associated with less postoperative pain, improved cosmesis and a more rapid return to physical activity and work than standard open hernia repair[1–3]. Although benefits of laparoscopic hernia repair have been described previously[4–8], many surgeons still doubt a superiority over traditional hernia repair[9–12]. To become generally accepted and to warrant the higher costs, new methods for hernia repair must be more effective than standard techniques.

A prospective study was designed to compare three currently used techniques of inguinal hernia repair with respect to postoperative pain, analgesic consumption, cosmetic result, experience with the type of operation and resumption of physical activity and work.

Paper accepted 19 January 1996

Patients and methods

Patients

A total of 86 consecutive patients having elective unilateral inguinal hernia repair were randomly assigned to one of three treatment groups. Randomization was done immediately before surgery in the anaesthetic room by use of sealed envelopes. Patients with recurrent or incarcerated hernia were excluded. Patients in group 1 had operations with the Shouldice technique ($n = 34$), those in group 2 underwent laparoscopic transabdominal preperitoneal (TAPP) hernia repair ($n = 28$), and those in group 3 had total preperitoneal (TPP) repair ($n = 24$) with a video-endoscope. The three groups were comparable with respect to age, sex, type of inguinal hernia and type of employment (*Table 1*). The study was approved by the local hospital ethics committee. Written informed consent to participate in the study was obtained from all patients.

Operative procedure

All patients in groups 2 and 3, and 13 in group 1, had surgery under general anaesthesia, where 21 patients in group 1 received spinal anaesthesia. Patients in group 1 had hernia repair by

Table 1 Patient details

	Shouldice ($n = 34$)	TAPP ($n = 28$)	TPP ($n = 24$)
Mean(s.d.) (range) age (years)	38·7(14·5) (17–63)	39·1(14·3) (21–63)	42·3(11·9) (20–62)
Sex ratio (M:F)	30:4	24:4	22:2
Type of hernia			
Direct	10	9	6
Indirect	24	19	18
Type of employment			
Light	8	8	6
Moderate	20	16	14
Heavy	6	4	4
Mean(s.d.) (range) length of hospital stay (days)	3·7(1·3) (2–8)	3·7(1·4) (2–7)	4·4(0·9)* (3–7)
Mean(s.d.) (range) duration of surgery (min)	38·4(9·7) (23–55)	46·0(9·2)† (28–60)	52·3(13·9)† (28–70)

TAPP, transabdominal preperitoneal; TPP, total preperitoneal. *$P = 0{\cdot}04$ (TPP *versus* Shouldice and TAPP), †$P = 0{\cdot}04$ (TAP and TPP *versus* Shouldice) means of the Shouldice technique[13] with continuous 0 polypropylene sutures. Patients in group 2 underwent laparoscopic preperitoneal hernia repair[14] with a polypropylene mesh (SurgiPro, Auto Suture, Vienna, Austria). Patients in group 3 had extraperitoneal repair[1] with a polypropylene mesh (SurgiPro). The surgeons performing the operations were experienced with all techniques of hernia repair and all the authors performed each of the three surgical procedures. No additional local anaesthetic was used during, or after, herniorrhaphy for pain control and no concomitant procedures were performed. Patients were discharged from hospital on demand and when there were no signs of systemic or local infection.

Assessment of postoperative pain and analgesic requirement

Preoperative and postoperative pain was evaluated by the patients using a visual analogue scale (VAS)[15] from 0 (no pain) to 10 (worst pain imaginable) on the first five postoperative days and on day 30 after surgery. Patients were instructed to ask for pain medication (intramuscular and oral diclofenac) liberally, as needed. Total analgesic consumption was recorded daily during hospitalization and then following discharge from hospital until patients were free from pain. After release from hospital patients were instructed to record pain and analgesic consumption at home.

Assessment of return to activities and work after operation

After hospital discharge all patients were encouraged to return to work and physical activity as soon as possible, when they felt comfortable. They were asked to record the return to 'pain-free' activity and work in a questionnaire given to them at time of discharge. The return to pain-free activity was preferred to recording simple return to activities because patients have different reasons for resuming activity. Variables used to assess physical activity were walking, driving, running, climbing stairs, bicycling, sports (tennis, skiing, climbing, soccer or squash) and sexual intercourse A clinical examination was scheduled 3 months after surgery and questionnaires were collected. At that time inquiries were made about further analgesia requirements, complications and patient satisfaction with the type of operation and cosmesis.

Statistical analysis

Variables measured on a nominal scale were analysed in the form of $2 \times k$ tables with the χ^2 test. When appropriate, Fisher's exact test or the χ^2 test (with Yates' correction for continuity) was applied to 2×2 frequency tables. The analysis of variables measured on an ordinal scale was made by means of Kruskal–Wallis one-way analysis of variance (ANOVA). If there was a significant difference between the groups, Dunn's multiple comparison procedure was used. Normally distributed (Shapiro–Wilks test) quantitative variables having the same variance in each of the groups (Levene test) were tested with one-way ANOVA. If the one-way ANOVA yielded significant results, the Scheffe multiple comparison procedure was applied. In case quantitative variables were not normally distributed and/or did not have the same variance in each of the groups, they were treated as variables measured on an ordinal scale (Kruskal–Wallis one-way ANOVA). All tests were two-tailed and made at a level of significance of 5 per cent ($\alpha = 0·05$). Analyses were done on a computer system (Superior Performing Software Systems; SPSS, Chicago, Illinois, USA) at the Institute for Statistics, University of Linz, Austria.

Results

The three groups were comparable with respect to age, sex, type of hernia and occupation (*Table 1*). Mean(s.d.) duration of surgery was longer in patients who had laparoscopic surgery (46·0(9·2) min) or the extraperitoneal approach (52·3(13·9) min) compared with 38·4(9·7) min for the Shouldice repair ($P = 0·04$).

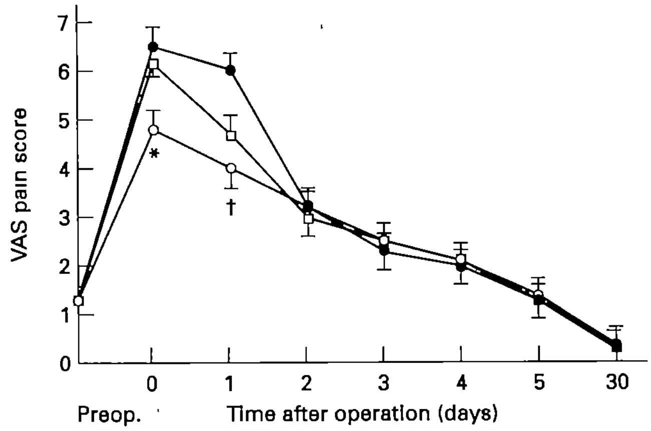

Fig. 1 Mean(s.e.m.) visual analogue scale (VAS) pain scores after laparoscopic transabdominal preperitoneal (TAPP; ○), total preperitoneal (TPP; ●) and Shouldice (□) hernia repair. *$P = 0·02$ (TAPP *versus* TPP and Shouldice); †$P = 0·01$ (TAPP *versus* TPP)

There were no intraoperative complications. Postoperative complications in patients having the Shouldice repair (group 1) included local haematoma (one), transient (three) and persistent (one) groin pain, and urinary retention (one). In patients who had laparoscopic surgery (group 2), there was one haematoma at the trocar site, persistent (one) or transient (three) groin or thigh pain, thigh numbness (two) and early recurrence (one), whereas in those having TPP repair (group 3) there was persistent (one) and transient (two) groin pain, epididymitis (one) and peritoneal tearing (two). Mean(s.d.) length of hospital stay was 4·4(0·9) days in group 3, which was significantly longer ($P = 0·04$) than in group 1 (3·7(1·3) days) or group 2 (3·7(1·4) days).

Postoperative pain and analgesic consumption

Mean preoperative and postoperative VAS pain scores are recorded in *Fig. 1*: Shouldice and TPP repairs were more painful than laparoscopic repair on the day of operation ($P = 0·02$). On the first postoperative day TPP repair was more painful than TAPP repair ($P = 0·01$), but thereafter there were no differences. Requirement for postoperative analgesia is shown in *Fig. 2*. Some 17 of 34 patients after Shouldice repair, 14 of 28 after TAPP repair and 4 of 24 after the TPP technique needed no analgesia during or after hospital stay.

Resumption of pain-free normal activities and work

The mean time to return to pain-free walking, running, climbing stairs, driving, bicycling and sexual intercourse was similar in the three groups (*Table 2*). Resumption of sports was a little earlier in patients operated on laparoscopically (group 2) and via the extraperitoneal approach (group 3) than in those having the Shouldice procedure, but was not statistically significant. Mean time off work was also similar in the three groups.

Satisfaction with the operation and cosmetic result

Patient satisfaction with the operation was comparable in the three groups (*Table 3*). Two of 86 patients (2 per cent

Table 2 Return to activity and work after inguinal hernia repair

	Shouldice (*n* = 34)	TAPP (*n* = 28)	TPP (*n* = 24)
Walking (days)	8·5(1·1) (2–21)	8·6(1·4) (2–21)	8·5(1·3) (2–21)
Running (days)	29·5(2·4) (12–60)	29·0(3·2) (3–60)	27·0(3·0) (7–55)
Climbing stairs (days)	13·0(1·2) (5–28)	12 3(1·4) (2–21)	14·2(1·2) (4–21)
Driving a car (days)	11·9(1·3) (4–28)	10·1(1·4) (2–21)	12·4(1·7) (3–25)
Sexual intercourse (days)	19·1(2·8) (4–42)	17·7(2·7) (3–40)	18·9(2·6) (4–40)
Bicycling (days)	29·6(2·9) (14–60)	26·6(2·2) (6–50)	27·4(2·7) (8–40)
Sports (days)	41·4(4·5) (14–70)	35·5(4 9) (4–60)	35·3(4·6) (15–60)
Return to unrestricted work (weeks)	6·9(0·7) (2–12)	5·9(0·7) (2–12)	6·5(0·7) (2–12)
Time off work (weeks)	4·8(0·6) (1–8)	4·9 (0·7) (1–8)	4 6(0·6) (1–8)

Values are mean(s.e.m.) (range). TAPP, transabdominal preperitoneal; TPP, total preperitoneal

Table 3 Comparison of outcome of hernia repair

	Shouldice (*n* = 34)	TAPP (*n* = 28)	TPP (*n* = 24)
Patient opinion of surgery			
Very satisfied	15	15	14
Satisfied	18	12	10
Not satisfied	1	1	0
Patient opinion of cosmetic result			
Very satisfied	19	19	17
Satisfied	14	9	7
Not satisfied	1	0	0
Recurrent hernia suspected			
Yes	1	7*	4
No	33	21	20

TAPP, transabdominal preperitoneal, TPP, total preperitoneal. *P = 0·02 (TAPP *versus* Shouldice, two-tailed Fisher's exact test)

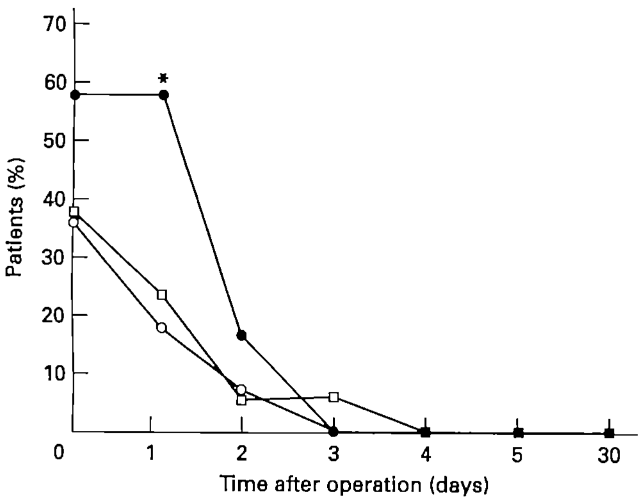

Fig. 2 Percentage of patients with need for postoperative analgesics following laparoscopic transabdominal preperitoneal (TAPP; ○), total preperitoneal (TPP; ●) and Shouldice (□) hernia repair. *P = 0·003 (TPP *versus* TAPP and Shouldice)

were not satisfied with the outcome of the operation, because of a long broad scar in one patient following Shouldice repair, and hernia recurrence in one having TAPP repair. A better cosmetic result was found with the TAPP and TPP procedures than after Shouldice repair. However, all but one of the patients having the Shouldice repair were either very satisfied or satisfied with the cosmetic result (*Table 3*).

Seven of 28 patients who had laparoscopic surgery (group 2), four of 24 having TPP repair (group 3) and one of 34 in the Shouldice group (group 1) self-reported a suspected hernia recurrence 3 months after surgery (*Table 3*). Clinical examination in these patients found only one recurrence in group 2 and none in groups 1 or 3.

Discussion

This study failed to demonstrate superiority of laparoscopic hernia repairs over the Shouldice technique. Return to physical activity such as walking, driving, climbing stairs, running, cycling and sexual intercourse, as well as return to work, was comparable in the three groups. However, there was a wide variation between individual patients, which depended on the advice of the general practitioner, personal motivation to return to work, information from colleagues who had had a hernia repair and type of occupation[4,16,17]. The type of occupation, which is regarded as one of the most important factors in determining outcome in terms of pain control and return to activity, was comparable in patients in this study. As found in other studies, employees returned later than the self-employed[17,18], but owing to the relatively small number of patients no evaluation was performed.

In this study the delay before return to work lagged far behind that of patients who have surgery for inguinal hernia in the USA, probably as a result of cultural and socioeconomic factors[17,19]. The prolonged convalescence in Europe is made possible through liberal disability coverage, resulting in low motivation of patients to return to work as early as possible. There were patients in all three groups who returned earlier to physical activity and often even to sports than to unrestricted work[16,18]. Consequently, it is important to motivate patients to an early return to work, irrespective of the type of hernia repair. The slow return to physical activity found in the present patients compared with that reported in other studies may be due to assessment of the time needed to resume pain-free activities, which may be more sensitive than return to activity.

The TAPP procedure caused significantly less pain than the TPP or Shouldice repair on the day of operation, whereas on the day after surgery no difference was found between Shouldice and TAPP repair. Patients having the TPP procedure, however, described more pain on the first two postoperative days, which was associated with higher analgesic consumption. Half of the patients having Shouldice and TAPP repair requested no postoperative analgesics, compared with only one-sixth of those undergoing the TPP procedure.

No explanation is available as to why some patients suspected hernia recurrence following laparoscopic and extraperitoneal hernia repair. Although only one recurrence was found following laparoscopic surgery, patients should receive postoperative information regarding this possibility and undergo postoperative clinical examination to exclude hernia recurrence.

In this study there were no significant benefits of laparoscopic herniorrhaphy compared with open hernia repair. The improved well-being described after laparoscopic herniorrhaphy is probably due to the cosmetic result, the enthusiasm for a new and attractive surgical procedure and the expectation of the patient, as well as of the surgeon. Although benefits remain to be proven for unilateral hernia repair, laparoscopic techniques may provide a more effective surgical alternative in the treatment of bilateral and recurrent hernias.

Acknowledgements

Statistical analysis was supported by a grant from Auto Suture Austria.

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British Journal of Surgery 1996, 83, 1567–1568

For debate

Ethical implications of recognizing nutritional support as a medical therapy

J. MacFie

Combined Gastroenterology Unit, Scarborough Hospital, Woodland Drive, Scarborough YO12 6QL, UK
Correspondence to: Mr J. MacFie

The fundamental tenets of medical ethics are usually considered to relate to the concepts of autonomy, justice and beneficence or non-maleficence. Autonomy is the pre-eminent theme in medical ethics today. It encompasses the philosophy that the individual has the right to determine his or her own destiny. A patient has the right to choose, the right to know and the right not to be harmed. Justice can be defined as the fair and equitable provision of resources to all. Patients are entitled to feel aggrieved if costs determine therapies. Beneficence, the concept of providing benefit, and non-maleficence, the avoidance of causing harm, are traditionally considered as part of the Hippocratic ethos. Beneficence and non-maleficence are not mutually exclusive and each should be considered separately in ethical debate. Accepting that this is a simplistic overview of an extremely complex subject, it is instructive to examine these principles of medical ethics as they apply to the use of nutritional support in different clinical situations.

Persistent vegetative states

The Tony Bland[1] and Cruzan[2] cases involved patients in persistent vegetative states whose survival was unquestionably dependent on artificial nutritional support. There is, therefore, no argument over the principles of beneficence or maleficence subject to the caveat that treatments deemed futile on the basis that recovery is impossible are considered by many as morally unjustified[3]. Notwithstanding this, the overriding factor in these cases, at least from the medicolegal point of view, is the principle of autonomy. The clinician must make a judgement as to whether or not the continuation or cessation of feeding would accord with the wishes of the patient if he or she was able to express a view. In reality, this necessitates surrogate decision-making by patients' relatives, the courts, or the implementation of previously expressed views in an advance patient directive or living will.

Critical illness

What of the patient admitted with critical illness of uncertain prognosis? For example, patients who have sustained a significant cerebrovascular accident, patients in intensive care units, those with major organ dysfunction, others with sepsis, neoplasia or infectious disease. In these, outcome, duration and prognosis may all be uncertain. As medical skills advance, such that patients who would previously have succumbed rapidly to their illness are kept alive longer, they survive to a point where undernutrition becomes the dominant factor in their chances of survival. In these clinical scenarios, as with the persistent vegetative state, there can be no argument that artificial nutritional support is justified on the basis of beneficence and maleficence. It is surprising, therefore, that adjuvant nutritional support is often not considered in these patients.

The principle of patient autonomy in the critically ill is determined by the issue of competence, that is, the ability of the patient to express a view. If unable to do so, the situation as described for patients with a persistent vegetative state exists. If, however, the patient can and does express an opinion then morally the doctor should abide by this. There are, of course, grey areas and the clinician is well advised to consider the concepts of competence and non-competence[4]. Where doubt exists it is reasonable to instigate time-limited trials of therapy such that, after a previously defined duration of treatment, the question of cessation or initiation of nutritional therapy is again assessed. The importance of recording these decisions in the case records is self-evident.

Malnutrition

Finally, what are the ethical issues that surround the treatment of the patients who are simply malnourished or who have sustained short periods of starvation? A major dilemma in this group is that there is no consensus as to the value of nutritional support therapies. Many clinicians remain unconvinced as to the benefits of nutrition, and remain reticent to advocate its use. This is surprising when one considers that just 10 days of inadequate oral intake will lead to significant alterations of physiological function and organ morphology in previously healthy adults[5]. This period is almost certainly less in ill, hospitalized patients in whom an inadequate intake of 7 days or less may affect outcome after surgery or influence the metabolic response to trauma, sepsis or neoplasia[6]. Nutritional support, be it as dietetic advice, sip feeding, enteral or parenteral nutrition can reverse the harmful consequences of inadequate intake with minimal morbidity[7]. What then is the ethical situation in those patients who have already been, or who are anticipated to be subjected to inadequate intakes of 7 days or more?

Considering the concept of beneficence there can be no doubt that nutritional deprivation does harm and that nutritional repletion by whatever means will prevent this, and presumably, therefore, it is reasonable to assume that the nutritional support therapy provides benefit. This conclusion is not invalidated by the many clinical studies that have failed to show benefit for nutritional support[8]. Absence of evidence is not evidence of absence[9]. These studies have almost invariably sought to prove alterations in clinical outcome following surgery or other therapeutic interventions in groups of patients with widely different disease processes. Nutritional therapy, like ventilatory or renal support, is not a disease-specific treatment and

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Based on a lecture given at the World Congress of Gastroenterology in Los Angles, California, USA, in October 1994, and published in *Nutrition* 1995; 11(Suppl 2): 213–16
Paper accepted 7 January 1996

assessment of benefit should, therefore, be based primarily on the correction or otherwise of nutritional abnormality.

What of non-maleficence in these patients? There is no doubt that certain techniques of nutritional support, such as inappropriate total parenteral nutrition, can be harmful[10]. This emphasizes the importance of the clinician tailoring the method of nutritional support that for a given patient will provide maximal benefit for minimal morbidity.

A consideration of the ethical principle of autonomy as this applies to the treatment of malnourished patients is less contentious. If patients were aware of the deleterious consequences of short-term starvation then it would seem reasonable to conclude that, if informed, they would request active measures to prevent harm. Unlike sophisticated medical therapies, patients understand the principles of nutritional support. The provision of food and water to the sick has a symbolic and an emotional role that transcends cultural, ethnic and socioeconomic barriers. Patients already ask about antimicrobial therapy and other well publicized treatments and will surely do the same with regards to nutrition therapy when there is a greater public awareness of the dangers of undernutrition, as well as an appreciation of the options for nutritional support. Recent reports in the media suggest that this is already occurring[11 12]. There may be patients who specifically object to artificial means of nutritional support and in these cases the wishes of the patient will have to be respected.

The resource implications of these observations are colossal. Not only is it well recognized that malnutrition in hospital is common but also recent studies suggest that almost 20 per cent of all surgical admissions may be subject to significant periods of inadequate intake[11,13]. These restrictions occur for several reasons and their effect is cumulative; repeated instructions for fasting before investigations, before and after medical or surgical intervention and as an integral part of treatment when 'resting the gut' is deemed appropriate. There is no reason to believe that episodes of inadequate oral intake would occur any less frequently on medical, geriatric or orthopaedic wards. The problem is compounded by changes in ward management and nursing practice that mitigate against the provision of meals or snacks for patients at any time outwith that designated by hospital policy.

Ethical implications

The implications of recognizing nutritional support as a medical therapy and of assessing its provision on the basis of accepted ethical principles are far-reaching. First, there would seem to be a sound philosophical argument that dictates that all patients who have inadequate intakes for 7 days or more should at least be offered advice on nutritional care. A documented dietetic referral may suffice. Second, failure to appraise and document nutritional status may, in the future, have medicolegal consequences. Third, there is an urgent need to raise the awareness of nutritional problems and their treatment in both medical and nursing professions[14]. Patients are asked about their bowel habit almost every day, and this is diligently recorded. Why not their food intake? Finally and most alarmingly, the financial implications of these recommendations are enormous. While dietetic advice, sip feeding and certain techniques of enteral nutrition are not in themselves expensive, the inevitable consequence of an increased awareness of nutritional problems will be an increase in the use of expensive nutritional support techniques. It is essential that inappropriate use of these latter techniques be minimized. This is probably best achieved by the establishment of nutrition support teams. These groups are best placed to monitor nutritional policy, to audit morbidity and costs and to ensure the most appropriate method of adjuvant nutritional therapy for individual patients. Surprisingly, only about 30 per cent of hospitals in the UK have access to a nutrition team[15].

In conclusion, the application of simple ethical principles to the use of nutritional support is likely to have a significant impact on clinical practice, particularly in Western society where the morality of different treatment strategies is increasingly subject to public scrutiny.

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British Journal of Surgery 1996, 83, 1569–1573

Fast-to-slow muscle conversion by chronic electrostimulation: effects on mitochondrial respiratory chain function with possible implications for the gracilis neosphincter procedure

D. F. ALTOMARE, D. BOFFOLI*, S. C. SCACCO*, M. RINALDI,
R. VICENTE-PRIETA, E. MARTINELLI and V. MEMEO

*Institutes of Clinical Surgery and *Medical Biochemistry and Chemistry, Università degli Studi di Bari, Bari, Italy*
Correspondence to: Dr D. F. Altomare, Istituto di Clinica Chirurgica, piazza Guilio Cesare, 11-70 124 Bari, Italy

The effects of chronic, around the clock, low-frequency electrostimulation on the respiratory chain activity and cytochrome content of freshly isolated mitochondria were evaluated in rabbit skeletal muscle before and after 30 days of continuous or cyclical electrostimulation using a totally implantable system and a training programme now used in humans. The respiratory activity measured in state III increased strongly after electrostimulation. The efficiency of the respiratory chain increased significantly after electrostimulation but the activity of complex I (reduced nicotinamide adenine dinucleotide dehydrogenase) did not increase. The amount of cytochromes *a* and *a_3*, *b_{562}*, and *c* and *c_1* increased clearly after electrostimulation. The respiratory activity rate of mitochondria obtained after continuous electrostimulation was apparently higher than after cyclical electrostimulation. Chronic uninterrupted low-frequency electrostimulation, using a clinical training programme, induces an increase in mitochondrial respiratory chain activity in purified mitochondria of skeletal muscle. These changes are the basis of induced resistance to fatigue in fast-to-slow muscle conversion by chronic electrostimulation.

The use of prolonged low-frequency electrostimulation of skeletal muscle has potential clinical applications.

The possibility of converting an easily fatiguable muscle into a fatigue-resistant one has been well known by physiologists since the 1960s, after the experiments with cross-innervation by Buller *et al.*[1] and chronic electrostimulation by Salmons and Vrbovà[2], but clinical application of this notion was introduced only in 1976, when the technique was applied to a rehabilitation programme following nerve injury[3]. More recently, in 1985, Carpentier and Chachques[4] have used it to assist cardiac function.

A few years ago the technique was applied successfully by Baeten *et al.*[5] and independently by Williams and co-workers[6] to construct a neoanal sphincter for the surgical treatment of faecal incontinence, using an electrostimulated gracilis muscle transposed around the anus.

Histological[7], histochemical[8] and biochemical[9] studies undertaken to investigate the changes induced in skeletal muscle by chronic low-frequency electrostimulation have shown that most type II fibres (fast twitch) can be converted into type I fibres (slow twitch), characterized by different structural and biochemical properties.

Although previous studies have analysed the increase in mitochondrial oxidative enzyme activity to parallel a reduction in the glycolytic capacity of skeletal muscle after chronic electrostimulation or exercise[10,11], few data are available on the changes in respiratory chain activity measured directly in purified muscle mitochondria. Further insights into the mechanisms of electrical fast-to-slow muscle conversion are essential for more efficient use of this procedure in clinical practice.

The aim of this study was to investigate the changes in mitochondrial respiratory chain function induced in rabbit skeletal muscle by chronic low-frequency nerve electrostimulation, using a training programme similar to that now used for converting the gracilis neosphincter by means of a totally implantable system[12]. A comparison between data obtained with two different protocols for chronic electrostimulation (continuous *versus* cyclical) was also made.

Materials and methods

Surgical procedure

Seven male adult New Zealand white rabbits weighing 3·5–4·2 kg were anaesthesized by intramuscular injection of Hypnorm (Duphar, Amsterdam, The Netherlands) 0·4 ml per kg bodyweight containing fluanisone 10 mg/ml and fentalyn 0·2 mg/ml. Under sterile conditions an Itrel Medtronic electrostimulator (model 7420) (Medtronic, Minneapolis, Minnesota, USA) was implanted subcutaneously and connected by an extension wire set to a four-plate electrode sutured to the nerve for the gastrocnemius muscle. The electrostimulator was then programmed telemetrically For biochemical analysis a biopsy was taken from the gastrocnemius muscle before electrostimulation and 30 days after the application of continuous (around the clock) low-frequency electrostimulation. The electrostimulator and the electrode were then removed. Three of the seven animals were allowed to recover and the entire procedure was repeated on the opposite leg to reduce intra-animal variation further. At the end of the experiments, the rabbits were killed with a lethal dose of anaesthetic. In two cases it was necessary to position a new electrode because the rabbits succeeded in opening the wound and biting the extension wires. Intramuscular antibiotic (200 mg cefuroxime) was administered once a day before operation and on the first postoperative day.

The animals were kept in cages and fed with pelleted rabbit food and water *ad libitum*.

Electrostimulation

Muscle electrostimulation was started on the second postoperative day and the electrical parameters were

Paper accepted 24 January 1996

programmed by a telestimulator (neuroprogrammer model T7454) according to two different protocols.

Continuous electrostimulation. The impulse width was 210 ms, the voltage was 0·5–1·0 V and the frequency was increased from 2 Hz for the first 10 days, to 5 Hz for the second 10 days and to 10 Hz for the last 10 days (24 h each day).

Cyclical electrostimulation. The impulse width was 210 ms, voltage 0·5–1·0 V, a fixed frequency of 10 Hz, an ON period of 2 s in the first week, 4 s in the second and third weeks, and always ON in the fourth week, and an OFF period of 4 s in the first and second weeks, and 2 s in the third week of electrostimulation (24 h each day).

In the three recovered rabbits it was possible to apply both protocols (continuous and cyclical electrostimulation) on the same animal on alternate legs. Allocation of the animals to one or other experimental protocol was at random.

Tissue processing

Biopsies of the gastrocnemius muscle (0·5–1·0 g) obtained before and after the period of electrostimulation were immediately processed to isolate mitochondria.

The muscle was homogenized in a medium containing 100 mg wet weight tissue per ml, sucrose 250 mmol/l, ethylenediamine tetra-acetic acid (EDTA) 2 mmol/l, Tris–hydrochloric acid 10 mmol/l and heparin 50 units/ml, final pH 7·4. Mitochondria were isolated according to the method of Bookelman *et al.*[13]. Mitochondrial proteins were determined according to Lowry *et al.*[14].

Polarographic measurement of oxygen consumption

Mitochondrial respiration rates were measured at 37°C in a thermostatically controlled micro oxygen chamber (YSI 5356, Yellow Springs Instruments, Ohio, USA) equipped with a micro oxygen probe (YSI 5357) coated with a standard membrane (YSI 5775). Proteins (0·10–0·25 mg) of freshly prepared mitochondria were incubated in 0·6 ml of a mixture containing sucrose 75 mmol/l, Tris-hydrochloric acid 30 mmol/l, potassium chloride 50 mmol/l, EDTA 0·5 mmol/l, magnesium chloride 1 mmol/l, potassium phosphate buffer 1 mmol/l, final pH 7·4. Respiration was started by adding different respiratory substrates (pyruvate plus malate, succinate plus rotenone, and ascorbate plus TMPD (N.N,N,^{1}N^{1}Tetra-methyl-p-phenylenediamine)) followed by the addition of adenosine 5′-diphosphate (ADP).

Measurement of reduced nicotinamide adenine dinucleotide–cytochrome c *reductase activity*

Mitochondria were disrupted by exposure to ultrasound at 0°C in a mixture containing mitochondrial proteins 23 μg/ml, potassium phosphate buffer, pH 7·4, 25 mmol/l, bovine serum albumin 2·5 mg/ml, magnesium chloride 5 mmol/l and cytochrome *c* 10 μmol/l. The suspension was supplemented with potassium cyanide 2 mmol/l and the reaction triggered by the addition of reduced nicotinamide adenine dinucleotide (NADH) 25 μmol/l. Reduction of ferricytochrome *c* was followed at 37°C at 550–540 nm, $\Delta\varepsilon$mmol/l = 19·1, in a Johnson Foundation dual-wavelength spectrophotometer. Activities were corrected for measurements determined in the presence of rotenone 2 μg/ml.

Measurement of succinate–cytochrome c *reductase activity*

Complex II was activated by preincubation of frozen–thawed mitochondria (5 μg protein per ml) for 30 min at 37°C in potassium phosphate buffer (50 mmol/l, pH 7·4) in the presence of succinate 20 mmol/l. The reduction of ferricytochrome *c* 9 μmol/l was followed at 37°C in the presence of rotenone 2 μg/ml and potassium cyanide 2 mmol/l.

Measurement of cytochrome c *reductase activity*

The ubiquinol–cytochrome *c* reductase activity was measured in frozen–thawed mitochondria (5 μg protein per ml) in a medium containing potassium phosphate buffer (50 mmol/l, pH 7·4), potassium cyanide 2 mmol/l and ferrocytochrome *c* 10 μmol/l. The reaction was started by adding duroquinol 30 μmol/l. Enzymatic activity was measured at 37°C following the rate of reduction of ferricytochrome *c*.

Measurement of cytochrome c *oxidase activity*

Cytochrome *c* oxidase activity was measured in frozen–thawed mitochondria (5 μg protein per ml) in potassium phosphate buffer (50 mmol/l, pH 7·4) at 37°C. The reaction was started by the addition of ferrocytochrome *c* 10 μmol/l.

Spectrophotometric determination of cytochrome content

For evaluation of cytochromes, difference spectra of cytochromes were recorded in a Lambda 5 Perkin–Elmer UV/Vis

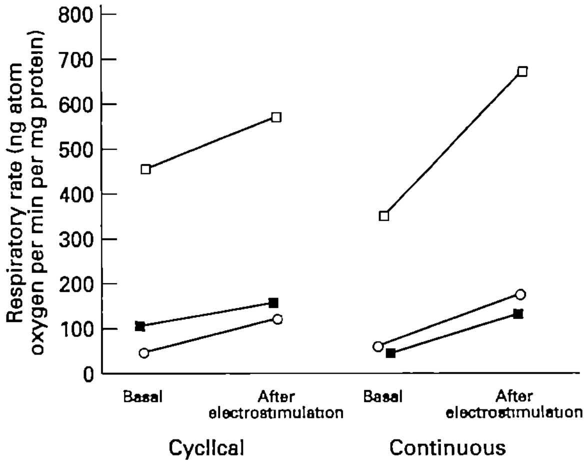

Fig. 1 Respiratory activity with different substrates after cyclical or continuous electrostimulation: ○, pyruvate and malate; □, ascorbate and TMPD (N,N,N,^{1}N^{1}Tetra-methyl-p-phenylenediamine), ■, succinate and rotenone

Table 1 Electrostimulation-related changes of respiratory rate in state III coupled in rabbit skeletal muscle mitochondria

	Respiratory rate (ng atom oxygen per min per mg protein)		
Substrate	Control muscle	Electrostimulated muscle	*P**
Pyruvate and malate (*n* = 8)	53(16) (38–69)	146(76) (83–210)	0·03
Succinate and rotenone (*n* = 8)	75(37) (40–110)	140(47) (99–180)	0·05
Ascorbate and TMPD (*n* = 8)	428(114) (302–524)	624(177) (476–773)	0·05

Values are mean(s.d.) (95 per cent confidence interval). TMPD, N,N,N^1,N^{1}Tetra-methyl-p-phenylenediamine. *Wilcoxon signed rank test spectrophotometer (Johnson Foundation, Pennsylvania, Philadelphia, USA) at room temperature, after reduction of cytochromes with succinate 20 mmol/l in the presence of potassium cyanide 2 mmol/l. Both the reference and the sample cuvette (optical pathway 1·0 cm) were filled with a suspension containing 0·3–0·5 mg mitochondrial proteins in 1·6 ml potassium phosphate buffer (75 mmol/l, pH 7·4), potassium chloride 187 mmol/l, Tris–hydrochloric acid 20 mmol/l, EDTA 4 mmol/l and magnesium chloride 5 mmol/l. For calculation of the mitochondrial cytochrome content the following extinction coefficients were used: cytochromes *a* plus a_3, $\Delta\varepsilon$mmol/l at 605–630 nm = 14; cytochrome b_{562}, $\Delta\varepsilon$mmol/l at 562–575 nm = 20; and cytochromes *c* plus c_1, $\Delta\varepsilon$mmol/l at 550–540 nm = 19·1.

Statistical analysis

Non-parametric statistical analysis for paired data (Wilcoxon signed rank test) was used to compare the results before and after electrostimulation.

Table 2 Muscle respiratory activity before and after continuous electrostimulation

	Respiratory rate (ng atom oxygen per min per mg protein)					
	Pyruvate and malate		Succinate and rotenone		Ascorbate and TMPD	
Experiment	T_0	T_{30}	T_0	T_{30}	T_0	T_{30}
1	63	248	58	129	417	896
2	53	132	21	138	185	518
3	89	126	23	73	301	463
4	29	220	84	153	520	826
Mean(s.d.) (95 per cent c.i.)	58(25) (19–98)	181(62) (83–280)	46(30) (−2–95)	123(35) (68–179)	356(145) (125–586)	676(217) (330–1021)

T_0, before electrostimulation; T_{30}, after 30 days of electrostimulation, TMPD, N,N,N,[1]N[1]Tetra-methyl-p-phenylenediamine; c.i., confidence interval

Table 3 Muscle respiratory activity before and after cyclical electrostimulation

	Respiratory rate (ng atom oxygen per min per mg protein)					
	Pyruvate and malate		Succinate and rotenone		Ascorbate and TMPD	
Experiment	T_0	T_{30}	T_0	T_{30}	T_0	T_{30}
1	42	53	120	69	322	502
2	59	89	138	188	532	761
3	38	231	68	193	466	441
4	53	74	91	174	561	588
Mean(s.d.) (95 per cent c.i.)	48(10) (33–63)	112(81)) (−17–240)	104(31) (55–153)	156(59) (63–249)	470(106) (301–640)	573(139) (352–794)

T_0, before electrostimulation; T_{30}, after 30 days of electrostimulation; TMPD, N,N,N,[1]N[1]Tetra-methyl-p-phenylenediamine, c.i., confidence interval

Table 4 Electron transfer rates before and after continuous or cyclical electrostimulation

		Electron transfer rate (mUnits per mg protein)							
		NADH–cytochrome *c* reductase (Complex I and III)		Succinate–cytochrome *c* reductase (Complex II and III)		Ubiquinol–cytochrome *c* reductase (Complex III)		Ferrocytochrome *c*–oxydase (Complex IV)	
Experiment	Electro-stimulation	T_0	T_{30}	T_0	T_{30}	T_0	T_{30}	T_0	T_{30}
1	Continuous	74	207	339	973	358	509	913	1885
2	Continuous	115	180	261	453	368	493	938	1786
3	Continuous	194	184	303	339	391	392	936	1360
4	Continuous	—	—	227	294	210	210	496	614
5	Cyclical	105	74	159	258	309	343	444	429
6	Cyclical	175	—	162	—	109	—	634	—
7	Cyclical	91	91	168	282	266	299	561	707
8	Cyclical	65	70	219	310	195	335	599	844
Mean(s.d.) (95 per cent c.i.)		117(44) (71–163) *P = n.s.	134(62) (69–200)	230(67) (173–286) *$P < 0.02$	416(254) (180–650)	276(99) (193–358) *$P < 0.03$	369(106) (271–467)	690(206) (518–863) *$P < 0.03$	1089(586) (547–1631)

NADH, reduced nicotinamide adenine dinucleotide; T_0, before electrostimulation; T_{30}, after 30 days of electrostimulation; c.i., confidence interval; n.s., not significant. *Wilcoxon rank sum test

Table 5 Cytochrome content before and after electrostimulation

	Cytochrome content (pmol per mg protein)					
	a and a_3		b_{562}		c and c_1	
Experiment	T_0	T_{30}	T_0	T_{30}	T_0	T_{30}
1	207	650	96	274	166	569
2	282	513	104	171	239	389
3	218	269	88	146	211	265
4	235	—	154	—	268	—
5	263	244	125	205	247	238
Mean(s.d.) (95 per cent c.i.)	241(31) (202–280)	419(196) (107–731)	113(26) (80–146)	199(56) (119–287)	226(45) (174–285)	365(151) (125–605)

T_0, before electrostimulation, T_{30}, after 30 days of electrostimulation, c.i., confidence interval

Results

Two of the seven rabbits did not complete the experiment: one persistently removed the electrode and the other died prematurely. As the operation was performed on both legs in three rabbits, a total of eight experiments were completed (four after cyclical and four after continuous electrostimulation).

The respiratory activity measured in state III (with ADP plus orthophosphate (P_i)), using pyruvate plus malate, succinate plus rotenone, ascorbate plus TMPD as substrates, markedly increased after electrostimulation (*Table 1*). The increase was higher with pyruvate plus malate (+175 per cent) and succinate plus rotenone (+87 per cent) than with ascorbate plus TMPD (+46 per cent). Although the mitochondria obtained from the electrostimulated muscle biopsies showed higher respiratory activity than the basal values in all cases, animals subjected to continuous electrostimulation had a higher respiratory activity rate than those having cyclical electrostimulation, particularly when using ascorbate plus TMPD as substrate (*Fig. 1*). The respiratory activity after each experiment of continuous or cyclical electrostimulation is shown in *Tables 2* and *3*.

The electron transfer rate from succinate to cytochrome *c* (complex II plus complex III), ubiquinol to cytochrome *c* (complex III) and ferrocytochrome *c* to oxygen (complex IV) were significantly increased after electrostimulation ($P<0.02$, $P<0.03$ and $P<0.03$ respectively), whereas the electron transfer rate from NADH to cytochrome *c* reductase (complex I plus complex III) was only slightly increased. These data, obtained in eight cases before electrostimulation (time 0) and in seven after electrostimulation (time 30), are given in *Table 4*.

Spectrophotometric analysis of cytochrome content, performed in five cases, showed that the content of cytochromes a plus a_3 and b_{562}, encoded by the mitochondrial genome, and of cytochrome c plus c_1, encoded by the nuclear genome, clearly increased after electrostimulation (*Table 5*).

Discussion

The results demonstrate that prolonged low-frequency muscle electrostimulation can induce an increase in the activity of the mitochondrial respiratory chain and in its cytochrome content. This increased efficiency of the aerobic substrates oxidation system to produce energy is a functional prerequisite for avoiding the development of fatigue during prolonged muscle contraction.

Previous studies have shown that periodic (6–10 h each day) chronic low-frequency electrostimulation of rabbit skeletal muscle induces histological, histochemical and functional changes in type IIA fibres, including increased capillary bed and decreased fibre size[15], synthesis of new myosin chains[16], modification of the reticuloendothelial system, changes in Ca^{++} sequestering and buffering capacity of the sarcoplasm (reduced parvalbumin and calsequestrin) and Ca^{++} pump adenosine 5′-triphosphatase[11], thicker Z discs and increased mitochondrial size[17], resembling some characteristic features of type I fibres. A comprehensive review of these data was made recently by Pette and Vrbovà[18].

Altered cytosolic Ca^{++} activity seems to induce an almost threefold increase in total RNA content, leading to the synthesis of new structural proteins (myosins) and an increase in the level of enzymes involved in oxidative energy metabolism[19].

So far, quantitative and qualitative changes in the enzymatic pattern of the muscle fibres after electrostimulation, including Krebs cycle enzymes, fatty acid oxidation enzymes and respiratory chain enzymes, have been documented histochemically or biochemically on centrifuged muscle homogenate, using prolonged but discontinuous muscle electrostimulation[9]. Hudlickà *et al.*[20] showed that the activity of citrate synthetase, 3-hydroxyacyl-coenzyme A dehydrogenase and succinate dehydrogenase activity increased twofold to threefold after 28 days of intermittent high-frequency (40 Hz) electrostimulation, and Reichmann *et al.*[21] were able to correlate similar or higher increased activity of citric acid cycle and fatty acid oxidative enzymes with ultrastructural changes occurring in rabbit muscle after 28 days of intermittent low-frequency electrostimulation (1 h on, 1 h off, for 12 h per day).

This study shows that chronic uninterrupted (24 h per day) muscle electrostimulation increases the efficiency of oxidation of all the three substrates and increases the activity of respiratory enzymes measured directly in purified muscle mitochondria. Unlike data reported by Reichmann and co-workers[21], the activity of complex I of the respiratory chain (NADH dehydrogenase) did not increase after electrostimulation.

The increase in cytochrome content after electrostimulation indicates that the increase in activity of succinate–cytochrome *c* reductase, ubiquinol–cytochrome *c* reductase and cytochrome *c* oxidase is associated with a rise in the content of haem a and a_3, cytochrome b_{562}, and cytochrome c and c_1.

Continuous and cyclical chronic low-frequency electrostimulation have been applied for a fast-to-slow conversion of the gracilis muscle used as a neoanal sphincter in incontinent patients[22]. Both methods gave good clinical results, expressed as fatigue resistance, but no biochemical investigations were carried out to compare the effects of the two modalities of electrostimulation on the enzyme energy pattern.

This study demonstrates that both methods are effective in inducing an increase in mitochondrial respiratory chain activity. Better results were obtained with continuous electrostimulation.

To the authors' knowledge, this is the first time these changes in mitochondrial metabolism, which can be considered the basis for induced resistance to fatigue in fast-to-slow muscle conversion by chronic electrostimulation, have been directly measured in purified mitochondria, in a model of electrostimulation that exactly resembles the protocols now used in patients.

Acknowledgements

This paper was supported by the Associazione Italiana per la Ricerca contro il Cancro. The authors thank Mrs Mary Pragnel for correcting the manuscript and Professor S. Papa for helpful comments

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British Journal of Surgery 1996, 83, 1574–1577

Pouch-related fistula following restorative proctocolectomy

F. PAYE, C. PENNA, L. CHICHE, E. TIRET, P. FRILEUX and R. PARC

Department of Digestive Surgery, Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, 75 012 Paris, France
Correspondence to. Professor R. Parc

Prognostic factors and outcome of pouch-related fistula were analysed from a series of 21 patients, 20 of whom had an ileal J pouch manually anastomosed to the dentate line following mucosectomy. Fistula occurred more often after pouch formation for ulcerative colitis than for familial adenomatous polyposis. In 6 patients the fistula occurred more than 5 months after closure of the diverting loop ileostomy. The origin of the leak was the anastomosis in 14 patients, the vertical staple line in two and the end of the efferent limb in five. Nine forms of treatment were utilized and these were successful in 11 patients and unsuccessful in ten including three pouch excisions. Adverse prognostic factors were late fistula, the presence of an enterocutaneous or a pouch–vaginal fistula track, and diagnosed or suspected Crohn's disease. Resolution of the fistula followed none of six diverting loop ileostomies performed alone, three of 33 attempted drainage procedures, four of ten direct closures, and four of five repeat ileal pouch–anal anastomoses. It is concluded that an aggressive therapeutic approach using repeat ileal pouch–anal anastomosis increases the success rate.

Proctocolectomy and ileal pouch–anal anastomosis (IPAA) is a widely accepted procedure for the surgical treatment of ulcerative colitis and familial adenomatous polyposis (FAP)[1,2]. Although rarely encountered, fistula originating from the ileoanal anastomosis or from the ileal pouch itself is a feared complication as it often requires further surgery, prolongs hospital stay and may alter ultimate functional outcome or lead to pouch excision. Data on the management of these fistulas are scarce and a large variety of treatments have been reported with variable outcomes.

A review was carried out of experience in the management of pouch fistula, in an attempt to identify prognostic factors and analyse the success rates of the different treatments utilized. The aim was to provide therapeutic guidelines that may improve outcome from this troublesome complication.

Patients and methods

Patients

Between 1984 and 1993, 373 patients had an ileal J pouch–anal anastomosis, 15 of whom (4 per cent) developed a pouch fistula. During the same period six patients were referred to this unit for treatment of this complication. The data on these 21 patients were reviewed and form the basis of this study.

There were six men and 15 women; the mean age at the time of initial operation was 34 (range 16–56) years Sixteen patients had ulcerative colitis, of whom two had undergone a previous ileorectal anastomosis, and five a three-stage IPAA for a severe attack of acute colitis. Of the five patients with FAP three had cancer in the colectomy specimen (one Dukes stage A and two Dukes stage B).

Surgical technique

Proctectomy, with excision of the distal rectal mucosa up to the dentate line and construction of a stapled ileal J pouch with a hand-sutured anastomosis to the dentate line, was performed in all but one patient who had a stapled anastomosis without mucosectomy in another centre and was referred for treatment of a fistula. All patients had a temporary diverting loop ileostomy. Two small suction drains were left in the pelvis lateral to the pouch and removed after 2–5 days.

Fistula assessment and follow-up

Fistulas were diagnosed clinically or visualized on routine pouchography. The origin and direction of the fistula track were assessed by ultrasonography and computed tomography (CT), examination under general anaesthesia, contrast enemas and fistulography. More recently magnetic resonance imaging (MRI) of the pelvis was employed to visualize the fistula track.

A data file was established for each patient which included the operative note, postoperative complications, time to fistula onset. symptoms, fistula site and each of the therapeutic procedures performed, with results The outcome was defined as successful if the fistula remained closed for at least 4 months after closure of the ileostomy. Follow-up was up to January 1995 for all patients.

Statistical analysis

Results were expressed as mean(s.d.). Comparison of qualitative variables was performed with the χ^2 test with Yates' correction.

Results

Six of the 21 patients developed a postoperative complication before the presentation of a fistula. One patient underwent reoperation on the third postoperative day for a pelvic haematoma, and two for small bowel obstruction. One anastomotic stricture required digital dilatation under general anaesthesia and two patients received antibiotics during the first postoperative month for sepsis of unknown origin. Diverting loop ileostomies were closed after a median period of 60 (range 54–106) days. The median delay between IPAA and fistula presentation was 5 months (range 10 days to 20 months) (*Fig. 1*). The diagnosis was made before ileostomy closure in six cases, while in 15, including the six patients mentioned above who developed a postoperative complication, the fistula appeared in the presence of a functioning pouch. Retrospective re-examination of the pouchograms performed via the loop ileostomy before closure in these 15 patients did not demonstrate any leak from the pouch or the anastomosis.

In this review, 13 (6 per cent) of 208 patients with ulcerative colitis and two (1 per cent) of 165 with FAP developed a fistula after IPAA ($P = 0{\cdot}02$).

Paper accepted 24 January 1996

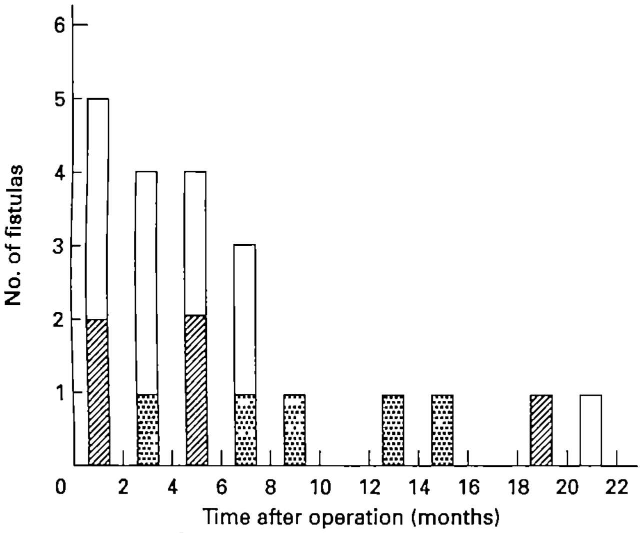

Fig. 1 Delay between ileal pouch–anal anastomosis and fistula onset in 11 patients with ulcerative colitis (□), five with Crohn's disease (□) and five with familial adenomatous polyposis (▨)

The principal symptom leading to the diagnosis of fistula was pelvic or abdominal sepsis or abscess in five patients, pelvic or perineal pain in two, impaired pouch function in two and external fistula in 12, of which four presented externally in the right iliac fossa, six presented via the vagina and two through the perineum. Four patients experienced recurrent pouchitis before fistula onset.

The origin of the leak was the anastomosis itself in 14 patients, the vertical staple line of the pouch in two and the end of the efferent limb of the J pouch in five. Fistulas exteriorized in the right iliac fossa resulted from leaks from the anastomosis (three patients), the vertical suture line (one) or the end of the efferent limb (one). All the pouch–vaginal fistulas resulted from anterior anastomotic dehiscence. Anastomotic stricture was associated with a pouch fistula in five patients, four of whom had a fistula originating from anastomotic dehiscence at the dentate line.

Nine forms of treatment were utilized to manage these 21 fistulas (*Table 1*). Overall, 62 procedures were performed, resulting in a mean of three (range 1–8) therapeutic procedures for each patient.

The final outcome of treatment was successful in 11 patients who had a functioning pouch without fistula recurrence (median follow-up from ileostomy closure 13 (range 4–104) months). The final functional status was good (three to six bowel movements per day, none or one in the night and normal continence) in six patients, intermediate in four (seven or eight bowel movements per day and two per night, or incontinence to liquid stools) and poor in one patient having ten bowel movements per day, one per night and incontinence for gas and liquid stools. Treatment was unsuccessful in ten patients. Three patients had the pouch excised. One of them, finally diagnosed as having Crohn's disease, still has a persistent perineal fistula track draining a residual pelvic cavity and another patient had an ileoperineal fistula which lasted 8 months before spontaneous closure. Four patients continued to have the pouch diverted because of a persistent external fistula, and three still have a non-diverted pouch with a productive fistula track.

Table 1 Procedures performed to treat ileoanal pouch fistula

Procedure	Covering ileostomy	Success rate*	Originating site of the cured fistula
Local dressing and irrigation	No	0 of 4	
Diverting ileostomy alone	No	0 of 6	
Perianal drainage	No	1 of 8	Anastomosis
	Yes	1 of 12	Anastomosis
CT-guided transgluteal drainage	No	0 of 4	
Drainage by laparotomy	No	1 of 5	End of efferent limb
	Yes	0 of 4	
Transanal fistula closure	No	0 of 1	
	Yes	1 of 2	Anastomosis
With gracilis interposition	Yes	1 of 2	Anastomosis
Fistula closure by laparotomy	No	1 of 2	End of efferent limb
	Yes	1 of 3	End of efferent limb
Repeat IPAA by laparotomy	Yes	4 of 5	End of efferent limb (2) Anastomosis (2)

CT, computed tomography; IPAA, ileal pouch–anal anastomosis. *Represented by the ratio of the number of fistulas remaining closed on a functioning pouch for more than 4 months to the number of procedures performed. Pouch excisions ($n = 4$) are not shown

There was no correlation between the initial disease and the final outcome. Successful outcome was obtained in three of five patients with FAP and in eight of the 16 who had ulcerative colitis.

The chance of cure was higher in patients with early fistula formation. A successful outcome was obtained in 11 of 15 patients who developed fistula before the 5th month after closure of the covering loop ileostomy, and in none of the six in whom the fistula developed more than 5 months after ileostomy closure ($P = 0{\cdot}01$). The success rate was similar whether the fistula occurred before or after closure of the diverting loop ileostomy. (Four of six *versus* seven of 15, P not significant).

Closure of the fistula was obtained in all five of the patients who presented with pelvic or abdominal sepsis but in only five of the 12 who had an enterocutaneous or pouch–vaginal fistula ($P = 0{\cdot}05$). Healing occurred in six of 14 patients with anastomotic fistula, in all of the five fistulas originating from the efferent limb but in none of the two originating from the vertical staple line of the J pouch.

The effectiveness of each of the therapeutic procedures performed and the originating site on the pouch of the successfully treated fistula are shown in *Table 1*. Local dressing and diverting loop ileostomy were attempted in eight patients and never succeeded. Some form of drainage (perineal or abdominal, CT-guided or surgical) was attempted 33 times in 15 patients presenting with pelvic or abdominal abscesses, and resolution of the fistula was obtained on three occasions. Direct closure of the fistula was attempted ten times in seven patients and succeeded on four occasions. To close the defect, the surgical approach depended on the site of the fistula. An abdominal approach was chosen to treat fistulas of the efferent limb by direct suture whereas a transanal approach was preferred to close anastomotic leaks by means of an ileal flap advancement technique or pouch dissection and advancement with a complete neoileoanal anastomosis. If previous treatment was unsuccessful, or if the fistula track was complex or of unknown origin on the pouch, an immediate repeat IPAA via an abdominal approach was chosen. This allowed full mobilization of the pouch and identification and repair of the defect. It was attempted in five patients and cured the fistula four times. In one case the reservoir was turned inside out so that the repaired bowel defect was hidden between the two leaves of the mesentery posteriorly, whereas intact bowel was brought in front of the former fistula track.

Crohn's disease was proven histologically in two patients and considered as the most likely diagnosis in three others because of ileitis or an ileal stricture located above the pouch. In these five patients, all fistulas occurred after ileostomy closure and four after the sixth month following IPAA (*Fig. 1*). Closure of the fistula was obtained in only one of these patients (repeat IPAA), but the functional outcome was poor. In another patient the reservoir was removed after failure of six successive attempts at drainage and repair, and the perineal wound persisted despite a muscular interposition graft. The three other patients still had a persistent fistula, one with a covering ileostomy.

Discussion

Pouch-related fistula formation occurred in 15 of 373 patients who underwent IPAA. This incidence of 4 per cent compares favourably with the 5–16 per cent reported in other series[1,3].

The frequency of pouch-related fistula was disease-related, in keeping with the findings of others who have reported a higher rate in patients with ulcerative colitis than in those with FAP[4]. However, the 6 per cent rate of fistula formation in patients with ulcerative colitis in the present study is low and may be a consequence of the widespread use of three-stage IPAA for severe attacks of colitis in the authors' institution. The three-stage procedure reduces the inflammatory process, allows reduction of steroid dosage and improves the nutritional status before IPAA, thereby decreasing the risk of subsequent pelvic sepsis and anastomotic leak[5,6]. Moreover, it may help in the diagnosis of Crohn's disease in some doubtful cases, thus decreasing the rate of IPAA for Crohn's disease and subsequent risk of fistula formation.

In many series the rate of pelvic sepsis and pouch-related fistula decreases with experience[3,7], suggesting that surgical technique plays a role in the occurrence of such complications. It is obvious that everything possible should be done to reduce tension at the anastomosis and septic contamination of the pelvic space. Reservoir design does not seem to be of importance[8] but a higher incidence of pouch–vaginal fistula was reported with the use of the two-loop pouch in one series[9]. The type of anastomosis may also play a role. In neither of two randomized trials comparing stapled and hand-sewn anastomosis was the risk of pouch-related fistula influenced by the type of anastomosis[9,10]. However, Groom *et al.*[11] found that the incidence of pouch–vaginal fistula after stapled anastomosis was twice that seen following suture. There is also some debate about the role of diverting loop ileostomy. In the authors' experience, this did not prevent fistula occurrence as six of 21 fistulas occurred before ileostomy closure and a normal pouchogram before ileostomy closure did not exclude a pouch fistula. There is no convincing evidence that loop ileostomy, which has its own specific morbidity, reduces the incidence or severity of pelvic sepsis and fistula formation[5,12–16].

Healing of the fistula was finally obtained in 11 of the 21 patients in this series and the functional status was acceptable most of the time, justifying the efforts made to save the pouch. This success rate is comparable with those reported in the literature for the treatment of pouch–vaginal[11,17] or pouch-related[3,18] fistula.

Crohn's disease was diagnosed or suspected in almost one-quarter of patients who developed a pouch fistula. Crohn's disease is a major cause of pouch-related fistula[3,19,20], especially when there is a preoperative feature suggesting the diagnosis[20]. Pouch fistulas complicating Crohn's disease are often difficult to treat and recurrence is common, frequently leading to pouch excision[3,17,20]. Crohn's disease should therefore be carefully excluded before operation and systematically suspected when managing a fistula following IPAA, particularly in cases of late fistula. Biopsies of the fistula track and ileal mucosa are mandatory before planning complex reconstructive surgery. Pouch excision may not always be curative, as in one of the present patients in whom a perineal fistula track arising from the distal ileum did not heal.

It is difficult to define a simple and didactic therapeutic approach towards a pouch-related fistula. The generally accepted policy is to begin with limited procedures such as drainage, correction of a stricture or re-establishment of a loop ileostomy, then to attempt local treatments such as endoanal ileal advancement flap or muscular interposition, and finally to proceed to repeat anastomosis or pouch formation before considering pouch excision[5,21,22]. In the present series limited procedures, even those carried out on a defunctioned pouch when the sepsis had settled, appeared unlikely to result in healing and delayed the institution of more aggressive treatment for several months. On the other hand, direct closure of the defect by a transperineal or transabdominal approach resulted in healing in four of ten occasions and repeat IPAA in four of five. These procedures should therefore be considered earlier. The chance of cure was higher in cases of early fistula formation, when there was no enterocutaneous track and when the fistula initiated from the efferent limb of the J pouch rather than from the anastomosis itself. It therefore seems important, before undertaking treatment of a pouch-related fistula to characterize its type precisely. Opacification of the fistula track, pouchography, CT and examination under general anaesthesia were helpful in this assessment. MRI has been used in a few recent cases; it seemed to be useful to locate pelvic collections accurately and fistula tracks are seen clearly on sagittal views. This preoperative morphological assessment could help as a prognostic indicator, may enable better evaluation of the efficacy of treatment, and may help to determine the surgical approach. For high fistulas with abdominal manifestations frequently originating from the efferent limb of the pouch, which generally have a good prognosis, an abdominal approach is necessary to suture the defect. For low fistulas, frequently originating from the anastomosis itself, an endoanal approach with an ileal flap advancement technique, or pouch advancement and neoileoanal suture as described by Fazio and Tjandra[22], would be appropriate and may be combined with muscular interposition[21] to fill a large pelviperineal cavity.

If the fistula track cannot be identified precisely or if previous therapeutic attempts have been unsuccessful, a more complex procedure with complete mobilization of the pouch by an abdominal approach to identify and close the defect is indicated. Repeat IPAA is carried out if the septic status of the pelvis allows. The authors have never had to employ a temporary disconnection of the pouch, because, in this series, repeat IPAA was always preceded by previous prolonged drainage of any septic collection.

These therapeutic guidelines may reduce the delay before ultimate closure of the fistula and increase the success rate with this rare but troublesome complication of restorative proctocolectomy.

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British Journal of Surgery 1996, 83, 1578–1580

Results after restorative proctocolectomy and ileal pouch–anal anastomosis in patients with familial adenomatous polyposis and coexisting colorectal cancer

Y. ZIV, J. M. CHURCH, J. R. OAKLEY, E. McGANNON, T. K. SCHROEDER and V. F. FAZIO

Department of Colorectal Surgery A111, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44 195, USA
Correspondence to: Dr J. M Church

Although the operation of choice for patients with familial adenomatous polyposis (FAP) is restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA), its place in the management of patients with FAP and cancer has not been defined. The authors have reviewed their experience with these patients to determine the safety of IPAA and its efficacy as a cancer operation. The records of 55 patients with FAP who had undergone IPAA were examined. Follow-up studies included an annual questionnaire and physical examination. Eight patients had FAP with coexisting colorectal cancer. Median age at diagnosis was 25 (range 13–46) years, and at operation 33 (range 22–36) years. Of the eight patients (four men), four had colonic cancer and four had rectal cancer. Synchronous colorectal carcinoma was found in two patients. Staging according to the tumour node metastasis classification showed that five patients had stage 1 tumour, two had stage 2 and one had stage 3. Tumours were well, moderately or poorly differentiated in one, five and two patients respectively. During a median follow-up of 56 (range 14–98) months, metastasis developed in the liver of one patient 66 months after surgery. Two patients suffered complications: one had small bowel obstruction and the other mucosal prolapse. Tubular adenomas were found in the pouch of two patients and in the anal transitional zone of one. Pouch function is good to excellent in all surviving patients. Restorative proctocolectomy for patients with FAP and coexisting colorectal cancer can be undertaken with a favourable prognosis and function. It is compatible with curative intent.

Familial adenomatous polyposis (FAP) is a rare hereditary disease characterized by the development of large numbers of adenomatous polyps in the colon and rectum. One or more of these polyps, in the absence of surgical intervention, will invariably progress to adenocarcinoma[1–3]. Until the advent of restorative proctocolectomy, the mainstay of surgical therapy for patients with FAP was colectomy and ileorectal anastomosis[2,4,5]. The surgical procedure of choice for patients with FAP and coexisting rectal cancer has been panproctocolectomy and ileostomy[2,5,6].

Restorative proctocolectomy with an ileal pouch–anal anastomosis (IPAA) for patients with FAP has become increasingly popular during the 15 years since it was initially described by Parks and Nicholls[7]. In comparison with colectomy and ileorectal anastomosis, it has a minimal risk for rectal cancer, while preserving anal defaecation, but it is a much more complex procedure often involving a temporary ileostomy[8–10]. Madden *et al.*[11] suggested that IPAA should be restricted to patients with large or confluent rectal polyps who are at higher risk of developing later rectal cancer, to those with curable colonic cancer at initial colectomy and to those unavailable for follow-up.

Despite these recommendations, there are few data concerning the place of IPAA in patients with FAP and colorectal cancer. Does radical resection of the colon and rectum influence pouch function? Does the pouch procedure alter cancer survival? To answer these questions, the authors reviewed their experience with patients undergoing restorative proctocolectomy with an IPAA for FAP and coexisting cancer.

Patients and methods

The records of patients undergoing IPAA between 1983 and 1992 were examined. During this time, 55 patients underwent restorative proctocolectomy with an IPAA for the treatment of FAP. Of these, eight patients (15 per cent) (four men) had colorectal cancer at the time of surgery. An additional three patients with cancer *in situ* (T_{is}) were excluded. Information was obtained regarding patient sex, age at onset of FAP, preoperative and postoperative pathological diagnosis, tumour location and the surgical procedure performed. The tumours were staged according to the tumour node metastasis classification.

The eight patients were surveyed for recurrent disease at 1, 3 and 6 months during the first year after surgery. Then, annual follow-up with a physical examination, estimation of carcinoembryonic antigen blood levels and personal interviews were carried out in the FAP registry of the Inherited Colorectal Cancer Registry in the authors' department. Chest radiography was performed annually and liver ultrasonography or computed tomography was done as needed.

Functional results (bowel movements per 24 h, use of antidiarrhoeal drugs, seepage and faecal incontinence) and quality of life were evaluated prospectively with a questionnaire and by physical examination. Quality of life was ranked by the patients on a scale of 1 to 10 (10 = excellent) in each of social, school and work activity, and dietary limitations. A score of 8 or more was counted as a good result. Pouch endoscopy and anal manometry were also performed routinely

Data are presented as the median and range where appropriate.

Results

The age at diagnosis of FAP and at surgery of 55 patients with FAP with and without coexisting cancer are shown in *Table 1*.

Indications for restorative proctocolectomy in the eight patients with FAP and cancer were a preoperative

Paper accepted 5 February 1996

diagnosis of cancer in four patients, high-grade dysplasia in one, villous adenoma in two and confluent rectal polyps in one. Three patients were under surveillance after a previous colectomy with ileorectal anastomosis (5–38 years). A completion proctectomy with IPAA was done. Five patients had a total proctocolectomy with IPAA. A hand-sewn ileal pouch–anal anastomosis technique was used in five patients, and a stapled technique in three with preservation of the anal transitional zone. All but one had a temporary ileostomy that was closed after 3 months.

Multiple synchronous colorectal cancer was found in two patients. The tumours were distributed as follows: one in the transverse colon (multifocal), three in the sigmoid colon and four in the rectum (multifocal in one patient). Staging and histopathological grading of the tumours are shown in *Table 2*.

Only two patients suffered complications; one had small bowel obstruction in the postoperative period that recurred later, and the other had mucosal prolapse into the anus. Tubular adenomas in two patients were found in the pouch at routine surveillance 1 and 5 years after surgery. Tubular adenomas in one of the three patients with preservation of the anal transitional zone were cauterized in the anal transitional zone 1 year after surgery. One patient with a stage 3 colonic tumour was treated with adjuvant chemotherapy. This patient developed a liver metastasis and a right lobectomy was performed 66 months after surgery. Her pouch function is good with mild seepage at night time (*Table 3*).

Table 1 Characteristics of 55 patients with familial adenomatous polyposis with and without coexisting cancer

	Patients with FAP ($n = 47$)	Patients with FAP and cancer ($n = 8$)
Age at diagnosis (years)	20 (2–59)	25 (13–46)
Age at surgery (years)	26 (12–60)	33 (22–36)
Follow-up (months)	27 (2–123)	56 (14–98)

Values are median (range). FAP, familial adenomatous polyposis

Table 2 Stage and histological differentiation of tumour in eight patients with familial adenomatous polyposis and coexisting cancer

TNM classification	Histological differentiation			
	Well	Moderate	Poor	Total
Stage				
1 (T_1, T_2, N_0, M_0)	1	3	1	5
2 (T_3, T_4, N_0, M_0)	0	2	0	2
3 (any T, N_+, M_0)	0	0	1	1*
4 (any T, any N, M_+)	0	0	0	0
Total	1	5	2	8

*Patient operated on for liver metastasis 66 months after surgery. TNM, tumour node metastasis

Table 3 Functional results in eight patients with familial adenomatous polyposis and coexisting cancer

Median (range) no. of bowel movements per 24 h	5 (2–6)
No. with seepage at night	3
No taking antidiarrhoeal medication	1
Quality of life (no. of patients grading this as 8–10)	7

Discussion

Restorative proctocolectomy with IPAA has provided satisfactory functional results in patients with FAP[6,8]. In theory, it should be possible to offer IPAA to patients with FAP and coexisting colorectal cancer as long as a radical cancer operation is performed. This study shows that this is the case.

Early and late complication rates in patients with FAP and coexisting colorectal cancer were low, and functional results and quality of life were good to excellent in all but one patient. Seepage at night is a common complaint[5,9,11] in patients after IPAA with a hand-sewn anastomosis and occurred in three of the eight patients.

After a median follow-up of 56 months, all eight patients are alive, although in one patient liver metastasis was discovered 66 months after surgery. This patient had a stage 3, poorly differentiated, colonic tumour, and was the only one who received adjuvant chemotherapy. The good survival (eight of eight patients) and low recurrence (one of eight) rates are explained by the early tumour stages at the time of surgery. Only one patient had stage 3 disease, presenting with symptoms. All four patients presenting while under surveillance had stage 1 disease.

Taylor *et al.*[12] reported satisfactory results with IPAA in four patients with FAP and 13 with ulcerative colitis complicated by adenocarcinoma, but did not differentiate between the two diseases in terms of prognosis and functional results. In a recent report from the same hospital on cancer complicating 34 patients with ulcerative colitis and 11 with FAP grouped together, Fozard *et al.*[13] reported satisfactory functional results and found IPAA to be an appropriate operation for those patients. Stelzner and Fonkalsrud[14] reported 12 patients with ulcerative colitis and two with FAP with coexisting cancer and concluded that, as long as the principles of radical surgery are adhered to, restorative proctocolectomy with IPAA is not contraindicated. These series[13,14], with the present findings, contradict Wiltz *et al.*[15], who advocated the use of initial resection followed by pelvic pouch construction after an initial observation period in patients with FAP or ulcerative colitis and a preoperative diagnosis of coexisting colorectal cancer.

Five of six patients with FAP and coexisting rectal carcinoma reported by Penna *et al.*[16] survived with no recurrence after a mean follow-up of 29 months. One patient with stage 4 disease died 6 months after surgery, and in one the pouch was removed because of diarrhoea and major night-time incontinence. Functional results were worse than in patients without cancer; this was thought to be related to mesorectal excision. The authors suggested that the poor functional outcome may lead to future pouch excision. The findings described here do not support this. All patients had a radical cancer operation with high ligation of all vessels and radical mesenteric excision, and the functional results were good.

Postoperative pelvic irradiation after IPAA was not given in the present series. Because of the susceptibility of small bowel to radiation damage, every effort should be made to avoid this treatment. Preoperative staging with ultrasonography and preoperative radiation for advanced cancer is a good strategy that will allow subsequent proctocolectomy with IPAA. Careful assessment of anal sphincter function is necessary before this can be advised, as radiation can damage the anal sphincters and predispose to incontinence after IPAA.

Restorative proctocolectomy for patients with FAP and coexisting colorectal cancer can be undertaken with a favourable prognosis and function and it does not compromise cure if an adequate tumour-free margin is obtained. The authors caution that all but one patient had early disease, and that these conclusions may not apply to patients with advanced rectal carcinoma.

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British Journal of Surgery 1996, 83, 1581

Surgical workshop

Resection of an end-colostomy stricture with a circular stapling device

J. M. RAMIA, A. IBARRA and J. ALCALDE

Servicio de Cirugia General y Aparato Digestivo, Hospital 12 de Octubre, Madrid, Spain

Correspondence to: Dr J. M. Ramia, C/Maternidad n°1 4°B, Ciudad Real 13 004, Spain

One of the complications of end-colostomy is stricture of the stoma as a result of local problems such as ischaemia, retraction of the distal portion of the colon, incorrect alignment of the mucocutaneous lip or infection[1]. Initially these strictures can be resolved by dilatation, but unfortunately reoperation is frequently necessary to create a new colostomy[1].

In 1986 Chung[2] described a technique to create an end-stoma with a circular stapler following abdominoperineal resection. In this paper a technique is described to reconstruct a stenosed end-colostomy with a circular stapler under local anaesthesia.

Surgical technique

A 56-year-old woman had an abdominoperineal resection for adenocarcinoma of the rectum. Six months later she developed a stricture of the end-colostomy, presenting with an external cutaneous opening with a diameter of only 5 mm.

The patient was given a local anaesthetic injection of 2 per cent mepivacaine hydrochloride around the stenosed end-colostomy. Four 10-mm long radial incisions were made around the stoma to allow dilatation of the stenosis and identification of the mucosal lip of the colon. Through this new orifice the anvil head of a 25-mm diameter circular stapler (CDH25; Ethicon España, Madrid, Spain) was inserted (*Fig 1*).

With a 3/0 absorbable monofilament suture, a purse-string was created around the mucosal colostomy lip and tightened around the anvil head of the circular stapler The radial incisions were partially closed with two sutures (*Fig. 2*). The circular stapler was assembled on the anvil head; some adjustment was needed to close the stapler because of fibrotic scarring (*Fig 2*). The stapler was fired and carefully withdrawn. A single doughnut was retrieved with an internal mucosal lip fixed to the cutaneous ring. The colostomy appeared to have a correct circular shape and a double line of staples in its periphery.

Paper accepted 16 December 1995

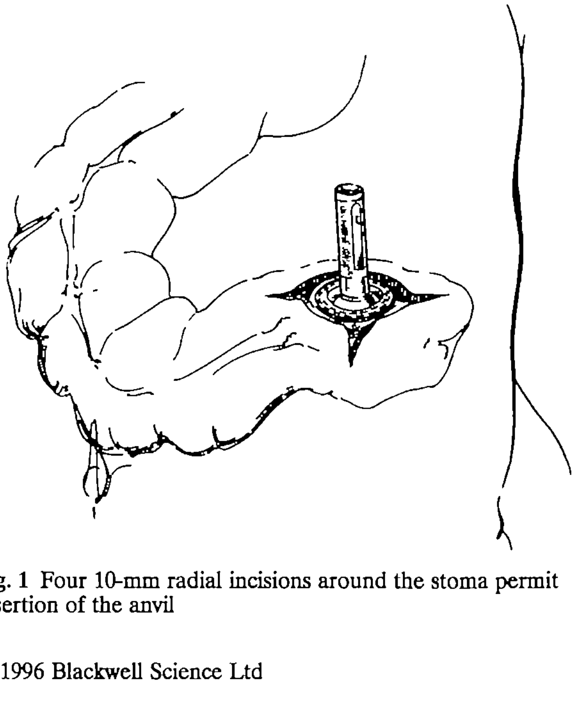

Fig. 1 Four 10-mm radial incisions around the stoma permit insertion of the anvil

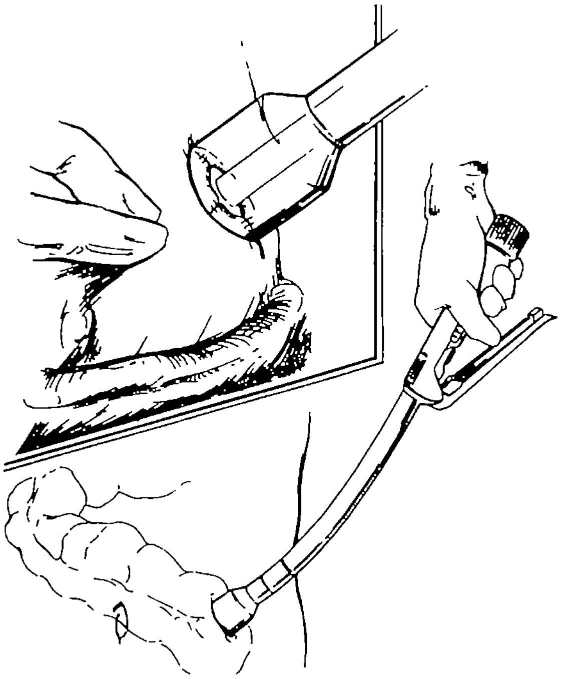

Fig. 2 The radial incisions are partly closed with two sutures; the stapler is then assembled and fired

The patient immediately received an oral diet and was discharged the next day. The staples of the cutaneous ring disappeared spontaneously within 15 days without adverse consequences. The stoma maintained an adequate diameter throughout the first postoperative year.

Discussion

This surgical technique can facilitate the treatment of a stricture of an end-colostomy, because the operation is performed under local anaesthesia with minimum risk to the patient and a hospital stay of less than 24 h.

The surrounding skin may initially appear oedematous owing to pressure of the stapler on the skin, but this resolves as the staples detach over the next 2 weeks.

Use of a circular stapler with a diameter greater than 25 mm is not recommended because it may be difficult to insert into the stoma, running the risk of damaging the mucosal lip. The 25-mm diameter circular stapler allows for excellent manoeuvrability of the colostomy.

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British Journal of Surgery 1996, 83, 1582–1585

Biomechanical stabilization of the nipple valve in continent ileostomy

K. W. ECKER, U. HILDEBRANDT, M. HABERER and G. FEIFEL

Department of General, Abdominal and Vascular Surgery, University of Saarland, 66 421 Homburg/Saar, Germany
Correspondence to: Dr K. W. Ecker

Despite stapler stabilization, sliding complications of nipple valve function occur in 19 per cent of continent ileostomies. Because the tendency of the ileum to desuscept is triggered by traction forces on the mesentery of the nipple during filling of the reservoir, a technique was developed to neutralize this biomechanical strain. In addition, to obtain fibrous healing between the muscular layers, the mucosa of contacting intestinal walls was removed by selective ultrasonic fragmentation. The valves of 18 consecutive patients were operated on with this technique. In six of these, a sliding valve was restabilized in a median time of 1·2 (range 0·4–2·9) years after conventional construction of the pouch. All are functioning well after a median of 4·6 (range 3·0–6·0) years. Between 1·8 and 4·8 years after operation a healed area between the musculature of the nipple and pouch of 4·5–7·2 cm² was shown by endosonography. This procedure may provide long-term prevention of sliding complications in continent ileostomies.

The continent ileostomy lost ground as the stoma of choice after proctocolectomy following the successful development of the ileoanal pouch as a better alternative compared with the incontinent ileostomy[1]. This might be one of the reasons that, despite remarkable technical improvements over the recent years, the stable nipple valve[2] has not received much attention. On the other hand, if continence is desired after ileostomy or failure of the ileoanal pouch, continent ileostomy still has a clearly defined place in the surgical armamentarium[1,3]. An attempt was made to improve the technique of primary construction with regard to stabilization of the valve based on the pathophysiology of desusception, and to clarify the morphological basis of the biomechanical effects by endosonography.

Patients and methods

Operative technique

The method established since the 1980s was modified so that invagination of the small intestine at the base of the nipple was kept in position by three rows of staples, but the fourth row of staples for fixation of the valve within the non-vascularized area to the pouch wall was abandoned. Instead the mucosa of the nipple was removed on the mesenteric side over a length of 5–6 cm and a width of 1–2 cm, and sutured to the posterior wall of the pouch by two parallel rows of suture. The suture material used was 3/0 nylon, the suture technique being continuous, all layer stitches at the margin of the mucosectomy. If a new valve was formed from the afferent loop of an already existing Kock pouch, this was made in an analogous fashion, refixation of the valve being performed without new staples being applied to the base of the valve (*Fig. 1*).

Mucosectomy was performed by selective ultrasonic fragmentation (Ultrasound dissector Sonoca, Soehring, Hamburg, Germany). With a working frequency of 23·5 kHz, ultrasound has a penetration depth of 300 μm in biological tissue[4]. Selectivity of fragmentation depends on the water content of the tissue and the applied energy (infinitely variable between 0 and 100 W); therefore the mucosa can be destroyed and the musculature preserved[4]. In initial trials with fresh human ileal preparations, the energy required for complete mucosal destruction was found to be 75 W. Histological examination showed no muscular damage with this energy level, if the ultrasound application was terminated at the level of the macroscopically visible complete mucosectomy A time of 10–20 s/cm² was necessary for complete mucosectomy

Patients

Between January 1990 and December 1992, 18 consecutive patients were operated on with the new method There were six men and 12 women of mean(s.d.) age at operation 38·8(10·6) years Fifteen patients had ulcerative colitis and three had familial adenomatous polyposis. The Kock pouch was initially established in nine patients (conversion of a Brooke ileostomy in seven), and in nine cases correction of valve instability was required following initial operation by the conventional technique (nipple prolapse three, gliding of the nipple six). The median period between the initial operation and the correction procedure was 1·2 (range 0·4–2·9) years

Follow-up

Patients were assessed with endoscopy and endosonography in October 1994. Configuration and healing of the nipple with the pouch wall were evaluated macroscopically by flexible endoscopy (Olympus GIF-Q20, Olympus Optical, Hamburg, Germany) in an inverted position. The diameter of the nipple was demonstrated at all levels from the base to the tip by endosonography (endosonographic probe BSK Medical, Naerum. Denmark; 7·5-MHz transducer with a millimeter scale at the probe) with an empty and a maximum water-filled reservoir. From the length and width of the healed zone between nipple and posterior area of the pouch, the total area of the healed zone was calculated (in cm²). Shortening of the nipple at maximum pouch volume was also measured.

Results

All operations were completed without intraoperative or immediate postoperative complications. Two patients were incontinent at the beginning of pouch training because of a fistula at the base of the valve. This fistula was closed by operation successfully after 4 and 5 months. During laparotomy and pouchotomy no relation between fistula formation and mucosectomy was found. Both fistulas had their origin at the beginning of the staple rows, where oversewing of the punch perforation of the leading mandril of the stapler was clearly insufficient. Complications resulting from instability of the valve

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Paper accepted 11 February 1996

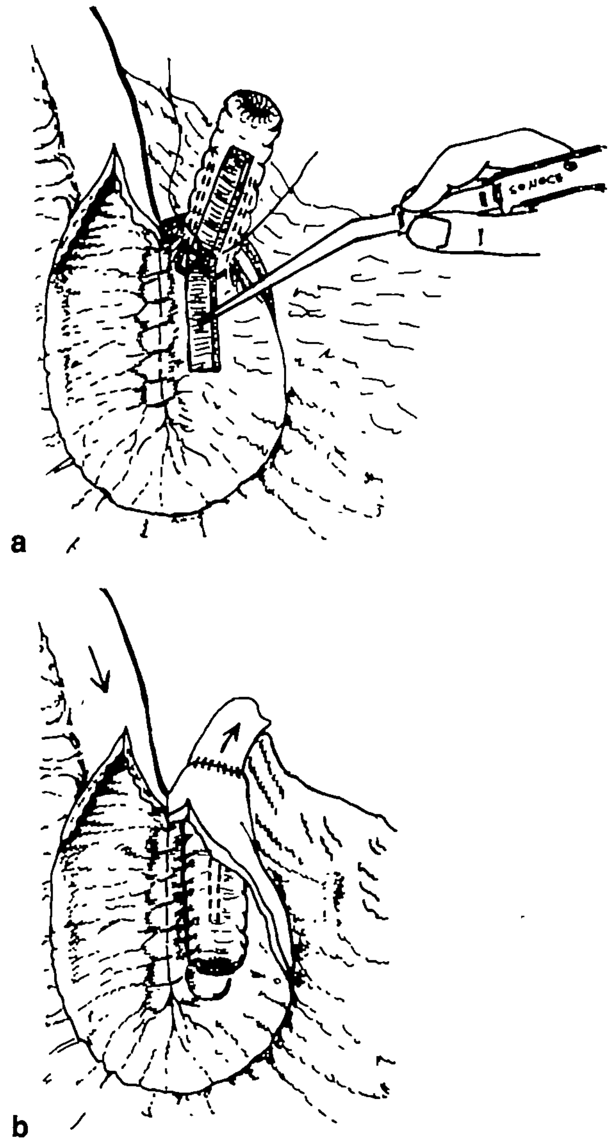

Fig. 1 Modified operative technique. a The invaginated nipple is held in place by three rows of staples in the non-vascularized circumference at the base. Ultrasonic mucosectomy is performed strictly in the area of the attached mesentery of the nipple and posterior wall of the pouch. The two continuous sutures (3/0 nylon) start at the end of the invagination and are sutured through all layers on both sides of the main mesenteric vessels. b Tension on the continuous sutures is adjusted under visual control of the circulation so that no ischaemia occurs. After completing the sutures, the nipple is broad-based along the whole length adjacent to the posterior wall of the pouch

(sliding or prolapse) were not seen in any of the 18 patients over a median period of 4·6 (range 3·0–6·0) years. All patients are continent.

Sixteen of the 18 patients were seen in October 1994. Endoscopy showed in all cases a broad-based adhesion of a normal-calibre nipple to the wall of the pouch. In 13 patients the nipple was measured by endosonography. The median length of the nipple with an empty reservoir was 46 (range 41–56) mm. After maximum water filling no shortening was observed. The area of adhesion between nipple and pouch wall was calculated within a minimum of 4·5 cm^2 and maximum of 7·2 cm^2 (median 6·3 cm^2).

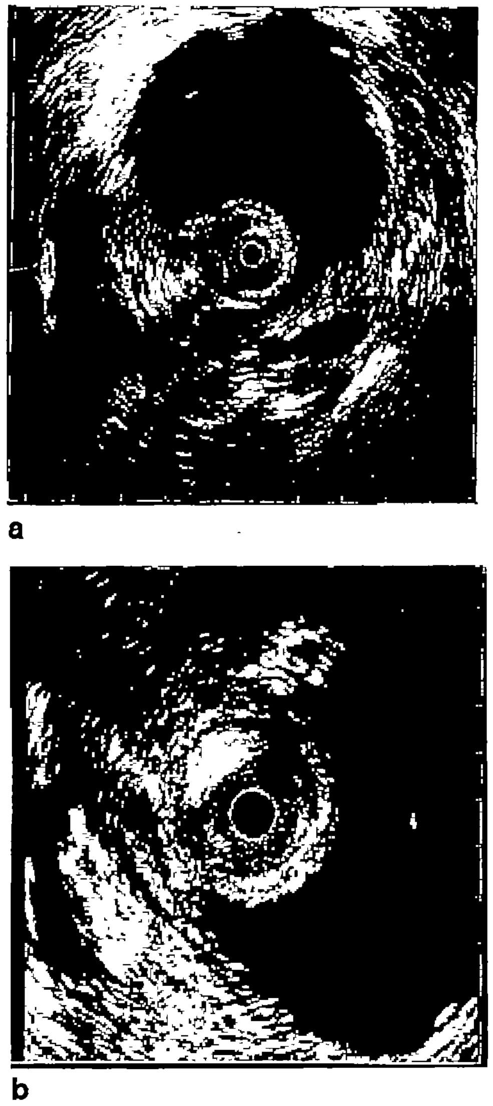

Fig. 2 Endosonographic cross-section of the continent ileostomy after suture fixation of the nipple to the pouch wall. During withdrawal of the endosonographic probe from a the tip of the nipple to b the base of the nipple, it can be seen that the nipple is adherent along its whole length and for about one-third of the circumference to the pouch wall. The echo-rich vessels of the nipple mesentery are clearly visible

Representative endosonographic cross-sections are shown in *Fig. 2*.

Discussion

Stable construction of the nipple valve required several modifications of the technique, so that the rate of late complications of malfunction could be reduced from an initial 50 per cent (even by Kock himself) to below 10 per cent[5]. The technical problem was the natural tendency of the invaginated small intestine to evaginate[6]; the stabilizing measures themselves also possess inherent risks of independent complications[2]. With the latest operative method which is based mainly on stapler stabilization of the base of the valve and stapler fixation of the nipple to the pouch wall, rates of up to 19 per cent and 2·6 per cent

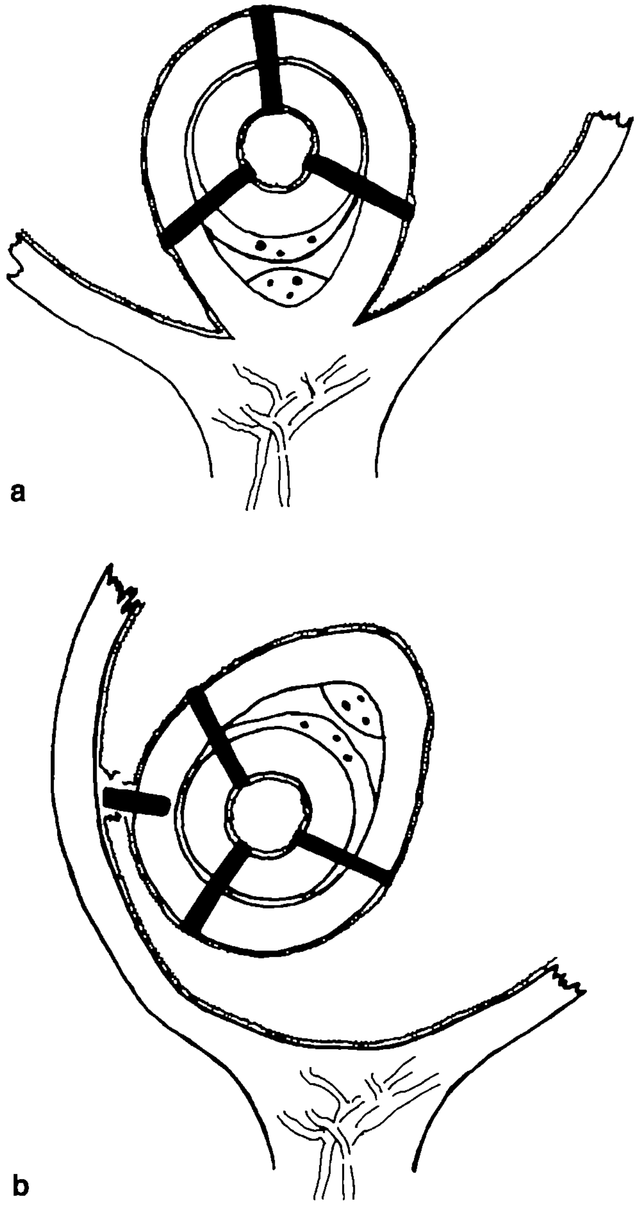

Fig. 3 Schematic cross-section through the Kock pouch. a With the modified technique the nipple is adherent within the area of the mesentery to the pouch wall. b With the conventional technique, the area of the nipple predisposed to instability floats freely within the pouch lumen. The stapled fixation to the wall of the pouch is weak and often tears out

are given in the latest large series for single complications of instability such as gliding and prolapse, and for stabilizing measures such as ischaemic necrosis and fistula formation up to 2·0 per cent and 7·1 per cent[5,7,8]. Biomechanical considerations of the pathogenesis of the nipple instability suggest that the traction forces applied during dilatation of the reservoir act via the intestinal wall to the base of the nipple and the mesentery to the tip of the nipple[6]. This results in extension of the invaginated nipple. The traction action begins at the area of the mesenteric attachment, where no spontaneous internal cicatrized healing of the nipple cuff can take place because of the interposed fatty tissue of the mesentery; neither can metal staples be applied because of the danger of ischaemia.

In view of the pathophysiology of the devagination and the unimpaired vascularization, the stapler technique was combined with the manual suture technique. With the aid of three staplers within the circumference of the non-vascularized nipple base, the internal and external ileal cuff were adapted precisely. Emphasis was placed in the stabilization procedures on fibrous healing of the muscle coat of the external nipple cuff with the wall of the pouch within the area of the respective mesenteric attachment, so that the forces applied during dilatation of the reservoir could be directed immediately to useful stretching of the nipple and not via the mesentery to an unfavourable traction point on the tip of the nipple. Mucosectomy by ultrasound and manual suture are requirements for maintaining the blood supply and thus for unimpaired healing. Unlike sharp mucosectomy, ultrasonic fragmentation also spares the vessels of the submucosa[4]. The advantage of manual suturing compared with stapling lies in the fact that traction on the continuous suture can be regulated according to the conditions of perfusion. By using non-absorbable suture material no disadvantage is to be expected with regard to stability compared with that produced by metal staples. The uncertainty of a mucosa-to-mucosa suture[9] is avoided by an all-layer suture. *Fig. 3* illustrates in schematic cross-section the essential difference between the new stabilization technique, with neutralization of the traction force within the area of the muscular scar between nipple and pouch wall, and the conventional stapling technique, with freely fluctuating nipple.

The postoperative clinical course fulfilled the expectations of the combined stabilization technique. So far no functional disturbances or other unexpected complications related to the new modification have been encountered. Statistical analysis has not been undertaken for two reasons. First, the number of patients with continent ileostomy is small[10] and, second, the two techniques, conventional and modified, have not been randomized. It is suggested that neutralization of the devaginating forces between the pouch and nipple is an effective technical principle. This may be supported by the endosonographic demonstration of a scar between the muscular layers. Scarification is facilitated by the ultrasonic mucosal fragmentation. This essential technical detail was suggested earlier by Kock, but has never been published (N. G. Kock, personal communication, 1990). However, the effectiveness of the removal of the mucosa could not be proven histologically because no further reoperations have been required thus far following stabilization of the nipple with the new modification. Sliding complications usually occur within 1–2 years[6], but in this series the patients with the shortest follow-up of 3 years are free from sliding problems. As with all other technical modifications, a longer follow-up will clarify whether this type of stabilization is an improvement or not.

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Announcement

A new course for the management of breast disease is launched by the College

In February 1997, a new and innovative training course for breast surgeons will be held at the College. The course is the first of its kind in Europe and is the result of cooperation between the Raven Department of Education and the Breast Surgeons Group of the British Association of Surgical Oncology (BASO), and has been made possible by generous Marks and Spencer plc sponsorship. The syllabus has been designed to cover all aspects of the curriculum laid down by the Specialist Advisory Committee (SAC) for specialist registrars with a subspecialty interest in breast disease.

Development

Under the chairmanship of Mr Michael Greenall, 12 course coordinators have been appointed by the Steering Group, who are responsible for the development and production of each core topic. The topics cover all aspects of breast disease, ranging from benign disease and primary treatment to ethics in practice, adjuvant treatment, research biology, screening, risk and reconstruction. The course and its handbook have been designed to encourage participants to consider contentious areas of clinical management, which will stimulate debate and facilitate assessment.

Organization

The teaching format will be both didactic and interactive, supported by over 50 faculties resulting in a high tutor:participant ratio. A broad-based format of clinical case scenarios, vignettes and multidisciplinary debates has been planned to encourage critical learning.

Teaching environment

Through a network of television links, participants will be able to observe a full range of procedures, including operations for benign breast disease, localization procedures, axillary surgery and breast reconstruction. Using the outstanding facility of the Hill Surgical Workshop, participants will be encouraged to consolidate their own experience with hand-on sessions using anatomical prosections and simulated models, in a structured and friendly learning environment.

Please contact the Course Coordinator, Kate Bowman, or her colleague Liz Woods, on 0171 973 2100, if you would like further details about the course. First course: 10–14 February 1997 inclusive; subsequent course: 27–31 October 1997 inclusive.

Dick Rainsbury FRCS
Course Tutor

British Journal of Surgery 1996, 83, 1586–1590

Problems in diagnosis and management of goitre in childhood and adolescence

A. J. WEBB, S. BREWSTER and D. NEWINGTON

Bristol Royal Infirmary, Bristol BS2 8HW, UK
Correspondence to. Mr A. J Webb, 7 Percival Road, Clifton, Bristol BS8 3LE, UK

This study is a retrospective review of 17 patients aged 16 and under with a total of 18 goitres, who were investigated and treated at Bristol Children's Hospital and Bristol Royal Infirmary between 1967 and 1994. There were five neoplasms, comprising follicular adenoma (three) and papillary carcinoma (two). Other benign causes of goitre included nodular goitre (four), non-toxic hyperplasia (three) and chronic lymphocytic thyroiditis (three). The authors suggest some guidelines to help in the diagnosis and management of goitre in young patients, as a consequence of significant difficulties encountered in 12 of the 17 patients in this series.

Goitres are uncommon in childhood and adolescence (up to and including 16 years), and malignant thyroid neoplasms are rare, being estimated at 0·19 per million population up to the age of 14 years and 3·0 per million between 15 and 25 years[1].

In 1957 Roberts[2] reported only seven patients with childhood thyroid carcinoma. A detailed review in 1974[3] collected ten patients under 20 years of age who had died from thyroid malignancy between 1957 and 1970 and analysed 25 young people registered with thyroid cancer in the UK between 1962 and 1967. Review of the pathology of 154 childhood thyroid cancers registered in England and Wales between 1963 and 1992 recorded an incidence of 0·5 per million children at risk per year[4]. Unlike some reports from North America[5–7], it would appear that no centre in this country will accumulate a large experience of goitres within this age group.

The purpose of this report is to review the variety of goitres operated on by two surgeons (H.R.N., A.J.W.), and to emphasize the problems encountered in the diagnosis and management of this condition.

Patients and methods

This study included patients under 17 years of age who had surgery for goitre at the Bristol Children's Hospital and Bristol Royal Infirmary between 1967 and 1994 inclusive. This placed emphasis well within the childhood age and minimal extension into adolescence. Both hospitals serve a local population of about 350 000 and since 1971 the children's hospital has been a Regional Referral Centre for Paediatric Oncology The anticipated yield of children (0–15 years) with all malignancies from the South Western Region (3·5 million population) is 66 per year. The Bristol Children's Hospital receives the majority of these and some others from neighbouring regions. Around 100 patients are treated annually.

Data were sought from operating theatre records, hospital notes, scintiscan and ultrasonic scan results, histopathology and both hospital and personal cytology files. The series was first presented in 1990[8] and was updated in 1994.

Results

A total of 18 investigated and surgically treated goitres were reviewed: 13 of the 17 patients (14 of 18 goitres) had been under the care of the senior author (A.J.W.) who had also performed the surgery. The clinical and other details are shown in *Tables 1* and *2*.

All histopathological (18) and cytopathological (11) material was retrieved and re-evaluated. In one patient (non-toxic hyperplasia), revision of the histopathology took 6 years to accomplish; the diagnosis was changed from atypical follicular adenoma to hyperplastic nodule. Whereas some of the data were retrospective, fine-needle aspiration cytology (FNAC) was performed in ten of the 18 goitres, and with the other tests constituted prospective management as the operative strategy was based on the summation of investigations.

Significant clinical problems arose in 12 of 18 goitres (*Table 2*). In the largest group this included a toxic follicular adenoma which was treated for some years as primary thyrotoxicosis. One patient had an unrecognized chronic lymphocytic thyroiditis (CLT) and in another a papillary thyroid carcinoma was mistaken for a 'puberty goitre'. The problem of surgery and histopathology was highlighted by a patient with an extremely rare variant of papillary carcinoma (diffuse sclerosing)[9,10]. The difficulty in separating true follicular neoplasms from 'pseudoadenoma' or non-toxic hyperplasia of childhood, first reported in 1961[11] was exemplified in two patients. Total lobectomy with identification of recurrent and external laryngeal nerves was performed for follicular adenoma (three), non-toxic hyperplasia (pseudoadenoma) (three), nodular goitre (one) and papillary carcinoma (one) (*Table 2*). The patient with diffuse sclerosing papillary carcinoma required three procedures: right lobectomy with isthmusectomy, completion total

Table 1 Surgical goitres in patients aged up to 16 years inclusive

	n	Mean (range) age (years)
Patients	17	
Goitre presentations	18	
Cervical node presentations	1	
Surgical operations	20	
Girls	16	14·8 (7–16)*
Boys	2	12 (8–15)
Histopathological specimens	18	
Cytopathological specimens	11	
Management problems	12 of 18	

*Median 13 years

Paper accepted 24 January 1996

Table 2 Details of patients, problems and outcome

Patient no.	Age (years)	Sex	Clinical presentation and year	Histopathology	Cytopathology procedure and result	Surgical operation and year	Problems and management	Outcome
1	11	F	Goitre 1968 L DN	Nodular goitre		L lobectomy 1968		FU by endocrinologists
2	15	M	Goitre 1967 MN	Nodular goitre	FNAC benign	Subtotal thyroidectomy 1967		FU 5 years
3	13	F	Goitre 1967 L DN	Nodular goitre		Subtotal thyroidectomy 1967		FU 2 years
4	7	F	Goitre 1988 R SN	Nodular goitre	FNAC benign	Excision nodule 1988	Clinical diagnosis and ultrasonographic scan errors	FU 6 months, then lost
5	12	F	Goitre diffuse 1970	Primary thyrotoxicosis		Subtotal thyroidectomy 1976		FU in Cornwall
6	16	F	Goitre diffuse 1980	Primary thyrotoxicosis		Subtotal thyroidectomy 1987	Clinical diagnosis ? toxic Hashimoto's disease. Large gland Failed protracted medical treatment	FU annually, on T4
7	8	F	Goitre 1970 R SN Hypothyroid	CLT	FNAC CLT	Biopsy nodule and isthmus		FU 5 years, on T4, moved away
8	13	F	Obscure illness 1988 L SN	? Riedel's thyroiditis		Incision biopsy L lobe 1988	Extensive investigations: ? vasculitis, mediastinal fibrosis TSH 250 milliunits/l Treated with T4	Died 1988 Cornwall, cause uncertain Post-mortem examination sugggested end stage thyroiditis
9	8	F	Goitre 1982 L DN	CLT		Partial L lobectomy 1983	Clinical diagnosis Atypical presentation Delay in T4 therapy	Recurrent goitre 1985, on T4
10	14	F	Goitre 1976 L DN	CLT		Incision biopsy 1982	Clinical diagnosis. Delayed recognition – atypical presentation	FU annually, on T4
11	16	F	Goitre 1980 R DN	Non-toxic hyperplasia	FNAC follicular adenoma? Hyperplasia?	Total R lobectomy	Interpretation of histopathology and cytopathology, emergence of non-toxic hyperplasia as an entity	FU annually, well during two pregnancies
12	16	F	Goitre 1984 R SN	(1) Atypical follicular adenoma (2) Non-toxic hyperplasia	(1) FNAC ? follicular adenoma ? hyperplasia (2) FNAC hyperplasia	Total R lobectomy Total L lobectomy	Interpretation of histopathology and cytopathology – expert opinion sought at each stage Initial view incorrect	FU annually, on T4
13	16	F	Goitre 1977 R SN	Toxic follicular adenoma	FNAC follicular adenoma	Total R lobectomy 1985	Clinical diagnosis – initially treated as primary thyrotoxicosis	FU annually, on T4
14	13	F	Goitre 1992 R SN	Atypical follicular adenoma and CLT	FNAC, SS, cystic follicular adenoma	Total R lobectomy and FS 1992	Thyroiditis not seen on FNAC smear, serum antibodies negative Histopathology problem	FU 4 monthly, on T4
15	16	F	Goitre 1992 R SN	Follicular adenoma	FNAC, SS benign follicular adenoma?	Total R lobectomy 1992	Clinical diagnosis and referral delayed 2 years	FU annually
16	8	M	R cervical 1988 lymph nodes and small goitre	Papillary carcinoma diffuse sclerosing variant	FNAC metastatic papillary carcinoma SS papillary carcinoma 1988	(1) Total R lobectomy and partial L, node excision 1988 (2) Completion total thyroidectomy 1988 (3) Excision metastatic nodes 1990	Unrecognized rare diffuse sclerosing variant. Difficult operative decisions Interpretation of histopathology and cytopathology. hitherto unique case	FU by paediatric oncologists On T4c Dec 1995 well Pubertal
17	16	F	Goitre 1992 R SN	Papillary carcinoma	FNAC, SS papillary carcinoma	Near total thyroidectomy 1992	Clinical diagnosis initially 'puberty goitre'. Given T4 therapy	Since 1994 rejecting T4 and FU

MN, multinodular; DN, dominant nodule within diffuse goitre, SN, solitary nodule, CLT, chronic lymphocytic thyroiditis; FNAC, fine-needle aspiration cytology, SS, scrape smear cytology from operative specimen; FU, follow-up, T4, oral Thyroxine sodium; TSH, thyroid-stimulating hormone, FS, operative frozen section; R, right, L, left

thyroidectomy and node dissection and, at an interval of 2 years, further excision of involved nodes. The other patient with papillary carcinoma was diagnosed before operation by FNAC. Near total thyroidectomy with node sampling was carried out. Partial lobectomy and excision of the nodule were performed for unilateral CLT and hyperplastic nodular goitre, respectively, and incision biopsy (isthmus 2, lobe 1) was done for three patients with thyroiditis: two had atypical CLT.

There were no reported complications. Postoperative recurrent laryngeal nerve function and voice quality was normal in patients who underwent major excision (nine). Hypocalcaemia did not arise in the patients having total and near total resections. Significant stress was experienced by the 8-year-old boy with papillary carcinoma and his family, consequent on three surgical procedures to clear the disease. Primary radical surgery may have limited this effect[12]. One patient, a 13-year-old girl who suffered a protracted and complex illness that defied precise diagnosis, died. A cervical swelling was present and incision biopsy material was reported as Riedel's thyroiditis. End-stage thyroiditis was suggested at post-mortem examination.

The five patients treated for neoplasm are under review, but one adolescent treated for papillary carcinoma has rejected both surgical follow-up and thyroxine (T4) treatment. One child developed recurrent papillary carcinoma and required a total of three operations. He has been disease-free for 5 years. The patients with non-toxic hyperplasia are subject to thyroid-stimulating hormone (TSH) suppression by oral T4 and regular review, as are the girls with CLT.

Discussion

Many of the reports from 1950 onwards concerning goitres in childhood refer exclusively to malignancy. Few are comparable with this group which records all surgical goitres over a period not dominated by irradiation sequelae. McHenry *et al.*[13] in 1988 assembled 65 patients under the age of 21 years. There were 24 carcinomas (papillary 63 per cent) of which 33 per cent had received previous therapeutic irradiation. The benign group ($n = 41$) included colloid nodules (40 per cent), follicular adenomas (33 per cent) and CLT (20 per cent). Another series[14] reported 42 benign goitres with a high incidence of follicular adenoma (17 of 42) and a single example of CLT. There were nine carcinomas (four papillary)[14].

Clinical examination of goitres is difficult and relatively inaccurate[15] so an investigation schedule or 'decision matrix' is important. This should include: standard blood investigations and thyroid blood levels (T4, tri-iodiothyronine and TSH), thyroglobulin and microsomal serum antibodies. In future serum thyroid peroxidase antibodies may be more sensitive[16].

Radiographs of the chest and thoracic inlet should be supplemented by ultrasonography. This may be more accurate in children than in adults[17]. Scintiscanning by ^{99m}Tc is retained by some[18] but rejected by others[15]. It may be definitive in a particular clinical situation: non-toxic hyperplasia can mimic follicular adenoma both at operation and histopathology. A hyperplastic nodule should absorb the isotope with avidity and outline other areas of hyperplasia, whereas a follicular neoplasm, benign or malignant, may not. If medullary carcinoma is suspected, then analysis of serum calcitonin and 24-h urine collection for catecholamines are mandatory.

For many surgeons FNAC is the investigation of choice for adult goitres and the same should apply in childhood and adolescence[19,20]. Up to the age of 10 years, a short general anaesthetic is helpful but, above that, local anaesthesia and sedation will suffice[21]. FNAC is preferable to large-needle biopsy[22]; it is less traumatic and more versatile. All patients in the present series investigated by FNAC ($n = 10$) received a diagnosis that matched the tissue diagnosis. Hyperplastic nodules (three) constituted a problem and were labelled 'follicular adenoma'. Histopathology on each occasion made the same error as cytology and this is an area in which ^{99m}Tc imaging may be helpful.

The preoperative identification of CLT was not achieved. In childhood and adolescence the presentation is often nodular or atypical[22,23] and the serum antibody status may be negative[21]. There is often no detectable evidence of altered thyroid function, merely a goitre. However, any child or adolescent with unexplained physical or mental illness requires a full investigation of the thyroid state and exclusion of 'cryptic' CLT. It should be possible to confirm CLT by FNAC and open biopsy is now regarded as avoidable[23]. Should the goitre not shrink on TSH suppression, or if the FNAC result is atypical, suggesting Hürthle cell neoplasia, then surgery is indicated. TSH suppression should be monitored over many years. If the goitre persists then epithelial or lymphoid neoplasia can develop, as it did in an 18-year-old woman not included in this series.

CLT was first comprehensively reported in 1954[23] and is largely confined to girls. As with adults it is seriously underdiagnosed and, with an increasing incidence, the problem is significant[22,24].

The five patients with a thyroid neoplasm were an important subgroup. At any age, the main aim of an investigation schedule is to identify neoplasms and malignant goitres. Three patients had a follicular adenoma: the first was a toxic lesion and recognized by clinical and cytological means. The others presented later in the series; preoperative FNAC was diagnostic and led to unilateral total lobectomy. Considerable diagnostic difficulty was associated with two patients with papillary carcinoma because the disease is so rare: 2–9 per cent of malignant tumours affect the thyroid in patients less than 18 years of age, around 10–15 per cent of head and neck malignancies in childhood. A 16-year-old girl had a 4-cm diameter papillary carcinoma and was diagnosed by FNAC. The other patient, an 8-year-old boy, was more complicated. He presented with cervical lymphadenopathy (40–80 per cent)[25,26] which was investigated elsewhere by incision biopsy and not FNAC. At exploration, the generally enlarged and firm gland was not recognized as the diffuse sclerosing variant of papillary cancer[9,10,27]. A total right lobectomy, with isthmusectomy, and node dissection was performed, but 50 per cent of the left lobe was preserved as it appeared to be less involved. This was a mistake; frozen section should have been sent from the resection margin[15]. Completion total thyroidectomy and further node excision was performed a month later with severe technical difficulty.

The importance of TSH suppression with oral T4 was demonstrated in this patient. The TSH was not reduced to immeasurable levels and nodes recurred in the right side of the neck. Further local node excision was performed over a year later. Diffuse sclerosing papillary cancer is extremely unusual. An estimate of incidence from the series of 154 registered cancers in England and Wales, at his age, lies at 1 per 300 million children/years. Overall only five examples were identified during 30 years[4].

Carcinoma of the thyroid in childhood and adolescence comprises 10 per cent of all thyroid cancers and a sizeable series will be assembled only from large referral centres[19,25,28,29]. Reports from Europe usually relate to small numbers of patients[30,31]. In such circumstances there is no choice but to heed large peer reviews and evaluate the controversies from personal experience[25,29].

Between 1920 and 1960 low-dose external head and neck radiotherapy was employed in North America for a variety of benign conditions. The causal relation between radiation and papillary thyroid cancer became widely accepted[6,7,13,32]. It was less often used in the UK and Europe, but isolated examples following multiple investigative radiographs occasionally appear. There is evidence that, in England and Wales, differentiated thyroid cancer is increasing[33] and concern exists over widespread contamination from nuclear accidents[34]. Computed tomography in infancy and childhood for staging procedures and craniocervical trauma is also a potential, but uncertain hazard. In this series, there was no history of irradiation in the five patients with neoplasm.

With the abandonment of irradiation therapy, the prevalence of differentiated thyroid cancer from 1945 onwards faded, with a tendency to less advanced tumours. A study covering the years between 1972 and 1984 produced 38 children in whom 27 goitres were benign (diffuse hyperplasia, nodular goitres, CLT) and 11 were malignant[35]; yet a recent report has revealed an aggressive form of papillary cancer termed 'solid follicular' affecting mainly the 5–9-year age range[4].

Papillary carcinoma is notoriously variable in its malignant potential and patients may survive for many years with controlled residual disease[36]. From an extensive literature some generally accepted areas of knowledge can be stated.

(a) The highest incidence of papillary cancer lies in the second and third decades; thereafter it evens out[18,27].

(b) Papillary cancer is 'biologically unfavourable' up to the age of 9 years. Between 9 and 16 years the good prognosis associated with the under-40 age group is assumed.

(c) At presentation most papillary cancers in childhood and adolescence are more advanced than in adults due to local invasion (5–10 per cent)[13,18], metastatic lymphadenopathy (70–90 per cent)[25,26] and pulmonary spread (5–10 per cent)[5]. Yet the response to treatment is better than in adults. Age alone is the most significant prognostic factor both in univariate and multivariate analysis[25].

(d) Recurrent papillary cancer, mostly in the form of nodal metastases, occurs in 13–20 per cent of patients up to 7 years after initial surgery. Reoperation is effective and there is no survival detriment[37].

(e) The unpredictable and protracted 'biological behaviour' of papillary cancer means that follow-up should be lifelong. Recurrence and death are reported up to 50 years after treatment[15].

(f) Controversy remains over surgical treatment for the primary tumour and the value of ^{131}I therapy. This dilemma exists in the age group up to 40 years and particularly the very young. Adults over 40 years have a relatively poorer prognosis so radical surgery is recommended. Nevertheless, not all young people with papillary cancer survive for 20 years and values between 85 and 100 per cent are quoted[38].

The radical approach[12,15] insists on total thyroidectomy with extensive nodal dissection[12] and radioactive ^{131}I manipulation in all patients, whatever age.

The conservative style epitomized by the publications of Crile *et al.*[39] and Cady *et al.*[40] is significantly different[26]. Surgery varies according to tumour size and extent. Total thyroidectomy is performed for bilateral tumours, otherwise limited surgery, even subtotal thyroidectomy or lobectomy, is acceptable[25]. Apart from patients with proven pulmonary metastases, ^{131}I is not favoured. Lymph node resection is limited to obvious abnormality, and thereafter a watching policy is adopted. Local excision is performed for nodal recurrence. TSH suppression with oral T4 is generally accepted.

The disadvantages of radical surgery relate to recurrent laryngeal nerve injury and permanent hypoparathyroidism. The latter is particularly difficult to manage in childhood[26]. Historically, reported rates of permanent nerve injury range from 6 to 22 per cent and that for the risk of hypoparathyroidism from 3 to 50 per cent[12,41]. A report from Sydney including 825 total thyroidectomies for benign and malignant disease quoted rates of 0·5 per cent for recurrent nerve injury and 0·6 per cent for permanent hypoparathyroidism[42]. The aim for many surgeons with less surgical experience will be to minimize both risks by near total thyroidectomy.

It is possible to preserve parathyroid glands at total thyroidectomy but function does not recover, presumably due to devascularization. Autotransplantation of one parathyroid gland has been recommended during total thyroidectomy[13]. Ideally, total thyroidectomy is suggested[15], as this will permit precise manipulation of ^{131}I to treat micrometastases and reduce the radiation load[12]. This may limit serious long-term pulmonary complications, particularly for the young.

The lessons from this small series suggest that goitre in childhood and adolescence should receive the benefit of joint management by paediatricians and endocrine surgeons, with an agreed protocol of investigation and management.

Acknowledgements

The authors are greatly indebted to Professor M. Mott, for referral of his patient (no 16) and much helpful advice, and Miss H R. Noblett, for allowing her patients to be included in the study. Professor J. Berry and Dr C. M. P. Collins enabled access to histopathology files and afforded assistance in the discussion of problems. The senior author (A.J.W.) was responsible for the cytopathology.

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British Journal of Surgery 1996, 83, 1591–1594

Reduced collagen accumulation after major surgery

L. N. JORGENSEN*†, F. KALLEHAVE‡, T. KARLSMARK§ and F. GOTTRUP‡

*‡Copenhagen Wound Healing Centre, Department of Surgical Gastroenterology, *Department of Urology, Hvidovre Hospital, †Department of Thoracic Surgery, Bispebjerg Hospital and §Department of Dermatology, Rigshospitalet, University of Copenhagen, Denmark*
Correspondence to: Dr L. N Jorgensen, Dyrehavevej 66, DK-3400 Hilleroed, Denmark

The preoperative and postoperative wound-healing capacity of 23 patients undergoing elective major abdominal, thoracic or urological surgery was tested objectively by the subcutaneous accumulation of hydroxyproline and proline in an expanded polytetrafluoroethylene (ePTFE) tube. Before scheduled surgery two ePTFE tubes were implanted for removal after 5 and 10 days. This was repeated for each patient immediately after surgery. After 10 days a higher amount of hydroxyproline was measured before than after operation (median 2·91 (range 0·37–14·45) *versus* 1·45 (range 0·26–6·94) μg/cm, $P = 0·01$)). This decline was significantly higher in the six patients who had a postoperative infection (median 3·02 (range −0·06 to 6·14) *versus* 0·36 (range −1·56 to 12·60) μg/cm, $P = 0·02$). This study shows that major surgery is associated with impairment of subcutaneous collagen accumulation in a test wound, suggesting diminished systemic wound-healing capacity in such patients.

Impaired wound healing in surgical patients results in increased morbidity and mortality. Although experimental animal studies on wound healing and trauma have been reported[1], the influence of major surgical injury on the general wound-healing process in humans is unknown because of the small number of models available for objective evaluation of the wound-healing process in humans. The subcutaneous insertion of tubes of expanded polytetrafluoroethylene (ePTFE) was reported by Goodson and Hunt[2] in 1982. They used GORE-TEX (W.L. Gore, Woking, UK) material with a pore size three times larger than that found in commercial vascular grafts. This produces a standard wound model in which ingrowth of inflammatory cells and fibroblasts takes place in the ePTFE mesh. A correlation between the accumulation of collagen in the ePTFE tube and the tensile strength of experimental animal skin wounds has been demonstrated with this method[3]. Depression of collagen deposition in ePTFE tubes has been reported in uraemia, malnutrition, dehydration, preoperative debility and illness, and secondary to treatment with corticosteroids[2–8]. Oral administration of arginine to human volunteers induces supranormal levels of collagen deposition in the ePTFE tube and an associated improvement in immune function[9,10]. In none of these studies did patients serve as their own controls.

The patient undergoing surgery is subject to a variety of factors that could lead to impaired healing. The wound-healing process is reflected by the amount of subcutaneous deposition of the amino acids proline and hydroxyproline. Hydroxylation of proline in the pro-collagen molecules results in the formation of a triple helical mature collagen molecule specifically rich in hydroxyproline[11]. The development of strength in a surgical wound is dependent primarily on the deposition of this mature collagen[12].

In this study the preoperative and postoperative accumulation of subcutaneous collagen was assessed in patients undergoing major elective surgical procedures.

Patients and methods

Patients

A prospective study was undertaken on patients who were referred for elective major abdominal, thoracic or urological operations (closure of colostomy or ileostomy (six patients), colonic resection (three), rectopexy (one), oesophageal resection (one), duodenotomy (one), pnemonectomy (three), pulmonary lobectomy (three), nephrectomy (four) and cystectomy (one). Patients who were aged less than 18 years, who were pregnant, who had undergone major surgery within 3 months, who suffered from uraemia, diabetes or allergy to local anaesthetics, or who were receiving corticosteroid medication were excluded Permission for the study was obtained from the Ethics Committee of Copenhagen. Written informed consent was obtained from each patient.

Twenty-five patients were included in the study. Two patients were excluded because surgery was cancelled as they were found to have widespread malignancy, leaving 23 patients for analysis Median age and body mass index of the patients were 67 (range 48–87) years and 24·1 (range 15 6–34·2) kg/m^2 respectively. The median (range) concentrations of haemoglobin, albumin, creatinine and zinc were 8·3 (5·6–10·1) mmol/l, 604 (375–747) μmol/l, 85 (56–157) μmol/l and 11·9 (7·5–15·4) μmol/l respectively.

Study design and implantation regimen

At least 11 days before scheduled surgery two 8·0-cm ePTFE tubes (High Porosity Tubing, product code OEM-012-01, IMPRA, Tempe, Arizona, USA) of inner diameter 1·2 mm, wall thickness 0·6 mm and pore size 90–120 μm were inserted subcutaneously in the mid dorsolateral part of the upper arm by means of a 2·5-mm cannula[13]. This was done under local anaesthesia with subcutaneous injection of 20 ml 1 per cent mepivacaine (Carbocain; Astra, Sodertälje, Sweden) The implants were placed in parallel, 3 cm apart. Approximately 1 cm of the tube was left outside the skin and covered with a transparent surgical dressing (Tegaderm, 3M Health Care, St Paul, Minnesota, USA). The ePTFE tubes were left implanted for a median (range) of 5 (4–7) and 10 (9–12) days. It was not possible to obtain an identical duration of implantation for all the patients in the preoperative outpatient period. The ePTFE tube implantation regimen was repeated at the time of surgery, when the patient was anaesthetized. The contralateral arm was used for implantation of the tubes. For each patient the

Paper accepted 16 January 1996

preoperative and postoperative durations of the ePTFE tube implantation were exactly the same, and the median time to removal of 5 and 10 days is used for descriptive purposes.

Following removal of the implants, 2-cm lengths from each ePTFE tube were placed in acetone and stored at 4°C for later hydrolysis in 6 mol/l hydrochloric acid for 12 h[13]. Measurement of hydroxyproline and proline was performed by comparison of peak areas referenced to known standards of hydroxyproline and proline using an automated spectrophotometric assay[14] The results were expressed as mass per length of ePTFE tubing (μg/cm).

Statistical analysis

Differences in proline and hydroxyproline deposition in the ePTFE tubes were evaluated by the Wilcoxon paired one-sample test. Unpaired results were compared with the Mann–Whitney two-sample test, and correlation was performed with Spearman's rank test. The tests used were two-sided with a 5 per cent significance level.

Results

There were no patient deaths within the first 30 days after surgery. Recovery within the 10-day postoperative follow-up period was uncomplicated in 15 patients. A 70-year-old man, who underwent oesophageal resection, experienced long periods of perioperative hypotension and cardiac arrest shortly after surgery. He was resuscitated and recovered completely. Six patients developed septic complications, verified by a positive culture or typical radiological abnormalities: these consisted of wound infection (one patient, who also had an anastomotic leak), urinary tract infection (one), pneumonia (one), pleural empyema (one) and intestinal anastomotic leak (three). One of these patients, a 73-year-old man, developed hypotension and severe hypoxaemia on postoperative days 3–5, and required reoperation on day 5. Compromised healing in terms of wound dehiscence with cutaneous fistula formation was observed in one patient. There were no local infections related to implantation of the ePTFE material. One patient developed a minor subcutaneous haematoma after removal of an ePTFE tube, without the need for surgical intervention. Another patient did not attend for removal of the ePTFE tube 5 days after surgery. This tube was removed after 10 days without analysis.

Significantly higher amounts of hydroxyproline were found in the ePTFE tube on day 10 than on day 5 after implantation, both in the preoperative and postoperative phases (*Figs. 1* and *2*). On preoperative day 5 the median (range) concentration of hydroxyproline was 0·81 (0·21–1·76) μg/cm compared with 0·77 (0·30–5·76) μg/cm on postoperative day 5 ($P = 0·4$). After 10 days of implantation the median concentration of hydroxyproline was significantly higher before than after operation (2·91 (0·37–14·45) *versus* 1·45 (0·26–6·94) μg/cm, $P = 0·01$) (*Fig. 3*). After 5 days of implantation the median (range) concentration of proline in the ePTFE tube was significantly higher in the preoperative than in the postoperative phase (93·6 (46·6–197·1) *versus* 63·9

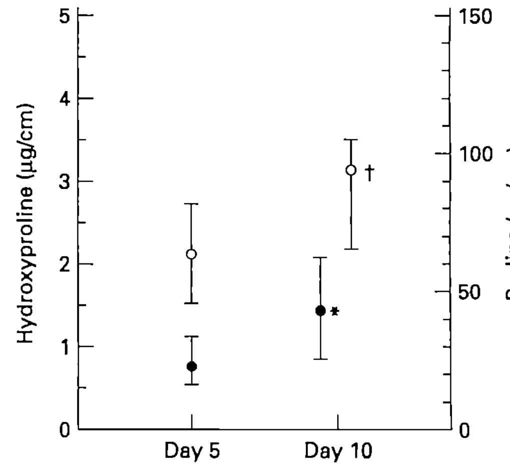

Fig. 2 Amounts of hydroxyproline (●) and proline (○) in expanded polytetrafluoroethylene tubes at days 5 and 10 after implantation in the postoperative phase. Values are median (interquartile range) $^*P < 0·005$, $^†P < 0·05$ (day 10 *versus* day 5, Wilcoxon paired one-sample test)

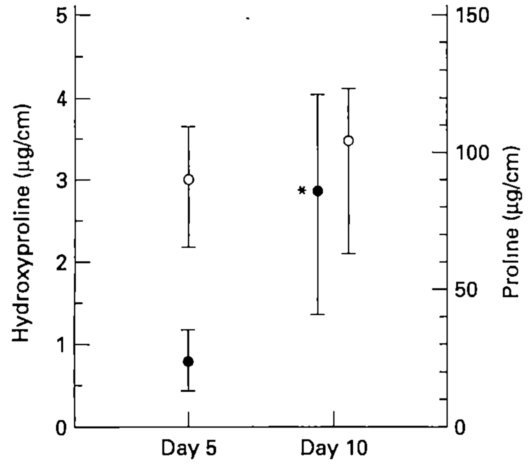

Fig. 1 Amounts of hydroxyproline (●) and proline (○) in expanded polytetrafluoroethylene tubes at days 5 and 10 after implantation in the preoperative phase. Values are median (interquartile range). $^*P < 0·00005$ (day 10 *versus* day 5, Wilcoxon paired one-sample test)

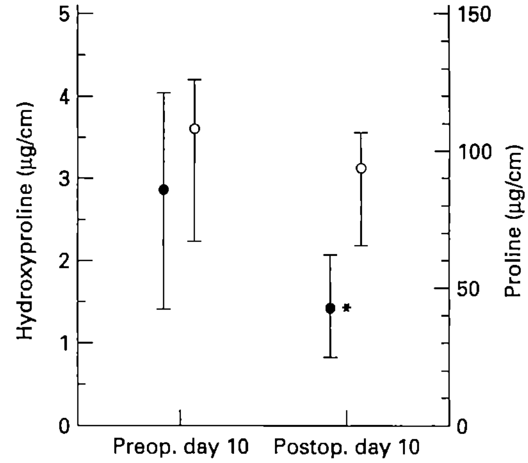

Fig. 3 Amounts of hydroxyproline (●) and proline (○) in expanded polytetrafluoroethylene tubes at day 10 after implantation before and after operation. Values are median (interquartile range). $^*P = 0·01$ (day 10 *versus* day 5, Wilcoxon paired one-sample test)

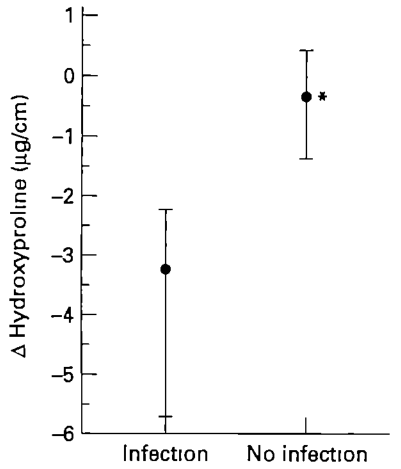

Fig. 4 Postoperative change in the accumulation of hydroxyproline in the test wound after 10 days in patients with postoperative infection ($n = 6$) and in those with no infection ($n = 17$) Values are median (interquartile range). $^*P = 0{\cdot}02$ (no infection *versus* infection, Mann–Whitney two-sample test)

(25·6–213·4) μg/cm, $P = 0{\cdot}01$). After 10 days of implantation no significant difference was found (109·4 (54·9–148·7) *versus* 95·1 (24·1–140·9) μg/cm, $P = 0{\cdot}22$) (*Fig. 3*).

Significantly lower postoperative amounts of proline were found after 10 days in patients with an infection than in uncomplicated patients (68·2 (54·3–98·1) *versus* 96·7 (24·1–140·9) μg/cm, $P = 0{\cdot}04$), whereas only a trend was found for hydroxyproline (1·19 (0·26–1·50) *versus* 1·80 (0·33–6·94) μg/cm, $P = 0{\cdot}22$). However, the postoperative decline in the amount of hydroxyproline in the test wound after 10 days was significantly more pronounced in the six patients who had a postoperative infection than in the 17 with no infection (3·02 (−0·06 to 6·14) *versus* 0·36 (−1·56 to 12·60) μg/cm, $P = 0{\cdot}02$) (*Fig. 4*). There was no significant association between the preoperative levels of hydroxyproline and proline and the occurrence of postoperative infection or anastomotic leakage.

None of the paraclinical preoperative assessments, or variables such as age or body mass index, correlated significantly with the amounts of hydroxyproline and proline after 5 or 10 days. The number of patients was not sufficient to allow any specific interpretation to be made of the predictive value of parameters such as smoking, malignancy, duration or type of surgery, or transfusion requirement on the postoperative accumulation of hydroxyproline and proline.

Discussion

With each patient serving as their own control, this is the first study to show directly that major surgery in humans is associated with early impairment of subcutaneous collagen deposition, reflecting a decreased healing capacity. This is in agreement with the report of reduced amounts of the collagen propeptides PICP (C-terminal propeptide of type I procollagen) and PIIINP (N-terminal propeptide of type III procollagen) in skin blisters during the first week after operation, indicating depressed collagen synthesis in peripheral skin[15]. However, measurement of collagen propeptides does not necessarily reflect the final amount of collagen deposited, as this is also influenced by the rate of collagenolysis.

Jönsson and colleagues[16] demonstrated that subcutaneous oxygen tension is often low in postsurgical patients despite adequate fluid maintenance according to standard clinical criteria including urinary output, and collagen deposition was determined by perfusion and tissue oxygenation[17]. This is supported by Hartmann *et al.*[18], who found that replacement of fluid according to close monitoring of subcutaneous oxygen tension improved the accumulation of collagen in the ePTFE model as dehydration was prevented.

Major surgery is associated with the release of catabolic hormones, vasoactive cytokines[15,19] and thrombosis-activating substances[20], which may eventually lead to proteolysis and impaired capillary perfusion. In addition the postoperative immune response is compromised[21], especially following perioperative whole blood transfusion[22,23]. This may result in compromised macrophage activation; macrophages are key cells in the formation and presentation of essential growth factors in wound healing[24,25]. One of the end-results of these pathophysiological mechanisms is reduced collagen formation.

The fact that the postoperative 'shutdown' of the accumulation of proline was observed on day 5 and not on day 10, as for hydroxyproline, may reflect the time sequence of collagen production in the early deposition of granulation tissue. The formation of hydroxyproline involves the hydroxylation of proline by prolyl 4-hydroxylase. If the rate of proline hydroxylation is reduced after operation, accumulation of proline will continue, perhaps explaining the similar values obtained for proline before and after surgery at day 10. The hydroxylation step, which is essential in collagen biosynthesis for the procollagen α-chains to form a stable triple helix, requires sufficient concentrations of molecular oxygen, ferrous iron, α-ketoglutarate and ascorbate[11,26]. Perioperative hypoperfusion[27], pulmonary-related oxygen desaturation, late postoperative sleep apnoea[28] and cardiac insufficiency result in tissue hypoxia, which is recognized as a cause of defective collagen biosynthesis[29].

The present results suggest that patients with septic postoperative complications have impaired collagen synthesis or an increased rate of collagen lysis. Again, this may merely reflect tissue hypoxaemia as a complication of infection or sepsis. Alternatively, depression of collagen formation could be a marker of other events related to sepsis such as impaired immune function or anastomotic leakage.

Using this ePTFE model for the quantitative evaluation of collagen formation, a degree of interpatient variation has been observed[13]. For this reason the present study was carried out with each patient serving as their own control, allowing for paired analysis. Local infiltration anaesthesia was used before preoperative insertion of the ePTFE tubes, whereas for the postoperative studies the tubes were inserted under general anaesthesia. This potential bias further supports the conclusion of the present study, as most publications report that the use of local infiltration anaesthetics impairs healing[30–32].

In conclusion, this study shows that major surgery is associated with impaired formation of collagen in subcutaneous granulation tissue, especially in patients with infectious complications.

Acknowledgements

The authors thank laboratory technicians Ole Christensen and Annie Høy. The IMPRA ePTFE material and other support were provided by Coloplast, Kokkedal, Denmark. The study was supported by grants from the Danish Medical Research Council (no 5.22.04.05), the Foundation of A. Louis Hansen and the Danish Hospital Foundation for Medical Research (Region of Copenhagen, The Faroe Islands and Greenland).

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British Journal of Surgery 1996, 83, 1595–1599

D_2 gastrectomy: lessons from a prospective audit of the learning curve

D. PARIKH*, M. JOHNSON†, L. CHAGLA*†, D. LOWE* and P. McCULLOCH*†

**Fazakerley Hospital, Aintree Hospitals Trust and †Department of Surgery, University of Liverpool, Liverpool, UK*
Correspondence to: Mr P. McCulloch, Department of Surgery, University of Liverpool, 5th Floor, UCD Building, PO Box 147, Liverpool L69 3BX, UK

A 3-year prospective study of the learning curve for D_2 gastrectomy was carried out by one surgeon beginning to perform the operation independently after intensive specialist training. Some 38 patients were treated; there were four postoperative deaths and 22 patients had complications. Postoperative morbidity decreased significantly with time ($r_S = -0{\cdot}38$, $P = 0{\cdot}02$, 95 per cent confidence interval $-0{\cdot}62$ to $-0{\cdot}07$). The physiological component of POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) was significantly lower in the third year (median value 15, 16 and 14 for years 1, 2 and 3, $n = 31$, $\chi^2 = 7{\cdot}5$, 2 d.f., $P = 0{\cdot}02$, Kruskal–Wallis test), but the operative POSSUM scores and the number of lymph nodes found were not decreased (median operative POSSUM score 19, 18 and 21, $n = 31$, $\chi^2 = 0{\cdot}2$, 2 d.f., $P = 0{\cdot}91$, Kruskal–Wallis test). The results suggest a learning curve lasting about 18–24 months or 15 to 25 procedures before a plateau is reached. Improved results were associated with changes in case selection and operative tactics but not with reduced extent of lymphadenectomy. D_2 gastrectomy should be restricted to specialist centres where adequate training and supervision can be provided during the learning curve.

The so-called D_2 gastrectomy was developed by Japanese surgeons for the treatment of gastric cancer. The operation involves a more extensive *en bloc* lymphadenectomy than is usually carried out in the West[1], and has been the subject of much controversy. Japanese surgeons have claimed significantly improved long-term survival in patients with stage II and III disease when this procedure is employed[2,3]. Western surgeons, on the other hand, have been concerned by the potentially increased morbidity and mortality associated with the D_2 procedure, which can involve resection of the spleen and distal pancreas when total gastrectomy is carried out. Recent trials in Britain and Holland have confirmed that the D_2 procedure is associated with greater morbidity and mortality than the lesser procedure (D_1) more typical of Western gastrectomies for cancer[4,5]. There are contrasting data from specialist centres in the West, which suggest that the D_2 operation can be carried out safely in Western patients[6–8]. The adequacy of the training of the Western surgeons involved in the randomized studies has therefore been called into question, and it has been suggested that some of the excess morbidity of D_2 gastrectomy in these trials may have been caused by a learning curve effect[9].

One of the present authors (P. McC.) began to perform D_2 gastrectomy unsupervised in 1992 after spending 4 months in Tokyo undergoing intensive training under supervision at one of the leading centres in Japan. By conducting a prospective audit of all D_2 gastrectomies performed by this one consultant the opportunity arose to study the learning curve from the beginning in an experienced surgeon. The main aim of this study was to estimate the length and 'height' of an individual learning curve for D_2 gastrectomy, that is, how many cases were required before a plateau of performance was reached, and how much improvement from baseline performance occurred during the process. In addition we hoped to evaluate the relative importance of changes in case selection, operative skill and operative tactics in bringing about any observed improvement. The POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) system[10] was used to evaluate preoperative and intraoperative factors that might influence morbidity and mortality.

Patients and methods

A prospective audit was carried from 1 June 1992 to 31 May 1995 of all cases in which D_2 gastrectomy was performed by one consultant surgeon (P. McC.). Data were acquired from the hospital case records as soon as possible after discharge of the patient and stored on a personal computer using a commercial database program (Framework III, Ashton Tate, California, USA, 1988). All cases of carcinoma or lymphoma of the stomach or cardia in which D_2 lymph node dissection was performed were included, whether or not the operation was ultimately regarded as potentially curative. During this period 31 patients with gastric cancer were seen in whom D_2 resection was not performed. The treatment of these patients, and the reasons for not performing D_2 resection, are given in *Table 1*. The POSSUM physiological and operative scores were calculated according to the formula described by Copeland *et al*[10], and the POSSUM program was used to generate a predicted risk in each case.

Patient data Hospital identification number, date of birth, sex, cardiorespiratory history, levels of urea and electrolytes, electrocardiographic findings, chest radiography findings, pulse and blood pressure on admission, Glasgow Coma Score on admission and preoperative weight loss were recorded prospectively.

Operative data. Type of operation (total or distal), date of operation, additional organs resected and incision used were recorded.

Tumour data. Tumour stage (Union Internacional Contra la Cancrum (UICC))[11], T stage, n stage, Japanese node stations resected[12], Japanese node stations involved by tumour, total number of nodes found and the total number of nodes positive for tumour were recorded. The individual Japanese node stations were dissected from the specimen by the consultant surgeon immediately after the operation, and placed in individual formalin containers. Specimens were then examined by the histopathologist without special clearance techniques.

Paper accepted 5 June 1996

Table 1 Details of patients not subjected to D$_2$ resection

	No. of patients	Additional factors*
Main reason for rejection		
T stage	7	Nodal stage (2), peritoneal metastasis (1)
Nodal stage	4	T stage (4), poor respiratory function (1)
Hepatic metastasis	5	Extreme cachexia (2), recent myocardial infarct (1)
Peritoneal metastasis	8	T stage (2), cachexia (2), nodal stage (1), age (1)
Unfit for surgery	5	Age (3)
Extreme age	1	T stage (early cancer)
Refused operation	1	
Total	31	
Treatment offered		
Palliative distal gastrectomy	2	
Palliative proximal gastrectomy	1	
Palliative total gastrectomy	3	
Devine exclusion	2	
Gastrojejunostomy	1	
Oesophagojejunal bypass (Roux en Y)	3	
Local excision of early gastric cancer	1	
Laparotomy and biopsy	3	
Laparoscopy and cytology/biopsy	7	
No operative procedure	8	
Total	31	

*These factors noted would in some cases have excluded the patient from consideration for D$_2$ gastrectomy (e.g peritoneal metastasis) but in others were contributory (e.g. the combination of extreme age and early cancer leading to the decision to perform a local excision)

Postoperative data. Postoperative stay in the intensive care unit (ICU), postoperative stay in hospital, death within 30 days, or in hospital during same admission, were recorded at the time of discharge.

The nature of any complications was noted; severity was recorded as minor, intermediate or major. Minor complications were those that had no impact on hospital discharge and were never thought to be life threatening. Intermediate complications prolonged hospital discharge by up to 1 month, but were not considered life threatening Major complications were those that either delayed ICU or hospital discharge by more than 1 month, or seriously threatened life or actually led to death.

Statistical analysis

Comparison of proportions was carried out by χ^2 testing. Comparison of POSSUM scores and morbidity by year was performed with the Kruskal–Wallis test and by Spearman's rank correlation; 95 per cent confidence limits were computed for each correlation coefficient. The Mann–Whitney *U* test was used where appropriate to test the significance of differences between year 3 and years 1 and 2 combined.

Results

There were ten D$_2$ gastrectomies in the first year, 17 in the second and 11 in the third, giving a total of 38 operations. Of these, 18 were total and 17 distal gastrectomies, while three were technically oesophagogastrectomies as they involved excision of more than 5 cm of thoracic oesophagus and a thoracic incision. The mean age of the patients was 64·4 years, and the male:female sex ratio was 29:9. The stage distribution according to UICC tumour node metastasis (TNM) criteria[11], and the nature of the operations carried out in each of the 3 years, are shown in *Table 2*, together with the number of cases that involved combined resection of one or more other organs, and the preoperative and operative components of the POSSUM score. Of 23 cases involving resection of additional organs, 11 involved removal of the distal pancreas and spleen; four of these patients also had parts of the oesophagus and diaphragm resected. Four cases involved splenectomy only, and two other patients had resection of more than 5 cm of thoracic oesophagus. In a further six cases the organs resected included transverse colon (two), gallbladder (three), a segment of liver (one) and adrenal gland (one).

There were four postoperative deaths in the series: two in the first year and two in the second year of the series. There were no deaths in the third year of the study. Complications occurred in seven patients in year 1, in 12 in year 2, and in three in year 3. The severity of the complications, whether they were associated with combined resection of pancreas and spleen, and the associated hospital stay are summarized in *Table 3*. There were four anastomotic leaks, two of which were detected by contrast radiology only. There was strong evidence of a trend towards decreased morbidity with time ($r_S = -0{\cdot}38$, $P = 0{\cdot}02$, 95 per cent confidence interval (c.i.) $-0{\cdot}62$ to $-0{\cdot}07$). The difference between the three years was significant ($\chi^2 = 6{\cdot}4$, 2 d.f., $P = 0{\cdot}04$, Kruskall–Wallis test),

Table 2 Operative details, physiological scores and staging in 38 patients having D$_2$ gastrectomy

	Year 1	Year 2	Year 3	Total
Operation				
Distal gastrectomy	6	8	3	17
Total gastrectomy	4	7	7	18
Oesophagogastrectomy	0	2	1	3
Combined resection	5 of 10	10 of 17	8 of 11	23 of 38
Stage*				
I	0	2	2	4
II	2	6	1	9
IIIa	1	2	1	4
IIIb	4	4	4	12
IV	2	2	3	7†
POSSUM‡				
Physiological	15·0	16·0	14·0	15·0
	(13–28)	(12–28)	(12–18)	(12–28)
Operative	19·5	18·5	21·0	19·0
	(17–26)	(14–27)	(17–23)	(14–27)
Complications				
None	3	5	8	16
Minor	1	3	1	5
Intermediate	3	6	2	11
Major	3	3	0	6

*Two patients had lymphoma and therefore were not staged by Union Internacional Contra la Cancrum gastric cancer criteria. †All patients with stage IV disease had T$_4$ tumours subsequently shown to be stage IV by virtue of nodal involvement; no patient with stage IV disease by virtue of hepatic or peritoneal metastasis was offered D$_2$ resection. ‡Median (range) value of Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity

Table 3 Morbidity associated with D_2 gastrectomy

Morbidity	No. of patients	Median (range) hospital stay (days)	Combined resection
Minor	5	10 (10–11)	Pancreaticosplenectomy (1) Splenectomy (2)
Intermediate	11	16 (12–28)	Pancreaticosplenectomy (4)
Severe	6	12 (4–51)*	Pancreaticosplenectomy (1) Splenectomy (2)

*Includes three patients who died on day 4

and direct comparison of morbidity in the third year with years 1 and 2 combined showed a highly significant reduction ($Z = -2{\cdot}5$, $P = 0{\cdot}01$, Mann–Whitney U test).

The median physiological (preoperative) POSSUM score was 15 in year 1, 16 in year 2, and 14 in year 3. The difference between the three years was significant ($n = 31$, $\chi^2 = 7{\cdot}5$, 2 d.f., $P = 0{\cdot}02$, Kruskal–Wallis test), and again the third year was significantly different from the other two ($Z = 2{\cdot}5$, $P = 0{\cdot}01$, Mann–Whitney U test). Spearman's correlation coefficient was $-0{\cdot}25$, $P = 0{\cdot}18$, 95 per cent c.i. $-0{\cdot}55$ to $0{\cdot}12$.

The operative POSSUM score measures the severity of the surgical insult: the median for years 1, 2 and 3 was 19·5, 18·5 and 21·0 respectively ($n = 31$, $\chi^2 = 0{\cdot}2$, 2 d.f., $P = 0{\cdot}91$, Kruskal–Wallis test). Spearman's correlation coefficient was $-0{\cdot}04$, $P = 0{\cdot}84$, 95 per cent c.i. $-0{\cdot}32$ to $0{\cdot}39$. The differences between years were thus not significant. Scores were not calculated in seven patients because of one or more missing data items. One of these patients was from year 1 ($n = 10$), two were from year 2 ($n = 17$) and four from year 3 ($n = 11$). Six had no complications, the seventh (from year 3) had intermediate complications. Overall four (31 per cent) of 13 patients with physiological scores lower than 15 suffered from intermediate or severe complications, compared with 12 (67 per cent) of 18 with scores of 15 or more. The best estimate of relative risk for intermediate or severe complications between the low and high POSSUM score groups is therefore 0·46 (31/67). The difference between groups with high and low POSSUM scores did not, however, reach significance at the 0·05 level (χ^2 with Yates' correction $= 2{\cdot}6$, 1 d.f., $P = 0{\cdot}11$).

The proportion of cases involving resection of additional organs increased from five of ten in year 1 to ten of 17 in year 2, and to eight of 11 in year 3 ($\chi^2 = 1{\cdot}17$, 2 d.f., $P = 0{\cdot}56$). In this series we found no association between resection of the spleen and/or pancreas and intermediate or severe complications: seven of 15 patients undergoing these additional procedures suffered from such complications compared with ten of 23 who did not.

The mean number of nodes found by the pathologist was 38 (range 25–67; nine patients) in year 1, 25 (range 4–65; 13 patients) in year 2, and 42 (range 29–52; nine patients) in year 3 ($\chi^2 = 7{\cdot}5$, 2 d.f., $P = 0{\cdot}02$, Kruskall–Wallis test). The third year was not significantly different from years 1 and 2 combined ($Z = -1{\cdot}4$, $P = 0{\cdot}15$). Spearman's correlation coefficient was $-0{\cdot}01$, $P = 0{\cdot}95$, 95 per cent c.i. $-0{\cdot}34$ to $0{\cdot}36$.

Of the patients who died, one elderly woman with chronic airway disease suffered from rapid cardiorespiratory failure following oesophagogastrectomy via a thoracoabdominal incision. One elderly man suffered from progressive multiple organ failure after an initial episode of arrhythmia and hypotension shortly after operation. A third elderly patient with known ischaemic heart disease suffered a sudden cardiac arrest 4 days after operation, following an initial smooth recovery. In none of these patients was evidence of leakage or sepsis noted. A 75-year-old man died from sepsis after leakage from an oesophagojejunal anastomosis.

Discussion

The D_2 gastrectomy remains controversial in the West because evidence of a survival benefit from randomized controlled trials is currently lacking, while evidence of increased morbidity and mortality has been obtained[4,5]. Reports from specialist centres, both in Japan and in the West, contradict these findings, suggesting that D_2 gastrectomy can be carried out with low morbidity and mortality. The training provided to surgeons entering both of the large multicentre trials of D_2 gastrectomy in the West has been criticized, and the suggestion has been made that much of the excess morbidity found with the D_2 procedure in these trials may have occurred during the 'learning curve' of this technically demanding operation. The present results strongly suggest the existence of a steep learning curve for an experienced surgeon beginning to perform D_2 gastrectomy independently, even after considerable preparatory training. The consultant who performed the operations in this series attended more than 30 D_2 operations in Tokyo as an assistant or observer, but had performed only two dissections under supervision before the start of the study period.

The present experience appears to conflict with that of the Dutch authors, who found no evidence of a learning curve[4]. Why should this be? Dutch trial participants received a very limited amount of practical training from a Japanese specialist: each 'supervising surgeon' was actually 'taken through' only one to three procedures before beginning to operate independently (M. Sasako, personal communication). The true number of D_2 operations performed by each supervising surgeon is unclear (the quoted figure does not tally with the overall total of D_2 operations). Given the limited initial training, the relatively low frequency of operations performed, and the variety of settings in which they occurred, it is tempting to speculate that a form of flattened learning curve may have prevailed during most of the study period. The experience reported here reflects the opinion of most Western surgeons with significant experience of the D_2 technique that specific training of adequate duration, and regular experience, are required to perform the operation safely.

The learning curve experienced in the present study appeared to plateau after 15 to 25 operations over a period of 18–24 months. What was it that was learned during this time? The likely explanations for the apparently improved results include better case selection, improved operative skill, better operative decision-making and reduced radicality (less extensive dissection). Analysis of the findings suggests that the last of these was not involved. The operative POSSUM score and the number of lymph nodes found showed no significant trend throughout the study period, suggesting that the extent of dissection was unchanged, and there was certainly no conscious decision to modify this. The apparent drop in lymph node yield in year 2 was due to incorrect application of the procedures for dissection of the specimen after operation in a few cases, and this was quickly noted and corrected. In fact, willingness to extend the operation to some n3 node stations has increased with time. The number of nodes found was similar to that in a recent large German series of D_2 operations[13], and reflects the method of dissection and harvesting of nodes from the specimen in the authors' institution.

Although the extent of lymphadenectomy did not change during the study period, operative tactics did. During this time the pancreas-preserving variant of the D_2 operation began to be performed wherever possible in cases of total gastrectomy because, in common with other European specialists[6,13], it was found that distal pancreatectomy was the most potent single source of complications in the procedure. No problem has been attributable to the splenectomy associated with D_2 total gastrectomy, and this continues to be performed. After experiencing significant respiratory complications with the thoracoabdominal route, an attempt is now made to avoid thoracotomy in patients with cancer of the cardia, by dividing the diaphragm to expose the lower mediastinum. Measurement of operative skill is difficult, but subjective confidence has increased while operating times have decreased during the study period.

Patient selection is generally considered to be one of the most important aspects of successful surgery. The negative aspect of this is that candidates who may be helped are denied operation. The initial selection criteria were extremely broad, encompassing all patients fit for laparotomy without obviously incurable disease (defined as malignant ascites, direct invasion of aorta, kidney or head of pancreas, peritoneal deposits outside the area of the main resection or nodal deposits in Japanese stations 13, 14 or 15). With time, these were modified to take account of the high prevalence of serious cardiorespiratory disease in the community and of better preoperative staging. This was reflected in the fall in the mean physiological POSSUM score in year 3. In view of the cardiorespiratory deaths seen in three patients, each of whom had caused preoperative concern because of the poor cardiorespiratory state, patients with significantly reduced exercise tolerance (less than one flight of stairs) should not be offered D_2 resection. There is no absolute age limit, but patients aged over 80 years must be free from overt cardiorespiratory disease as well as meeting the exercise tolerance criterion. An evaluation is currently being made of the usefulness of a POSSUM physiological score criterion of fitness for this operation. Data suggest that the risk of significant complications rises steeply once the physiological score passes 15, but this estimate will require independent validation in a further prospective audit. The increased use of staging laparoscopy has improved the authors' ability to detect incurable disease before operation, but this has not affected policy because such disease discovered at laparotomy leads to the performance of only a D_1 operation (or no resection).

Audit of personal practice in surgery is often difficult to interpret because of the problems of accumulating sufficient cases for statistically meaningful analysis in a reasonable period of time. It may nevertheless prove useful to others to reflect on the lessons learned here. Operating time appears to be of much less significance than blood loss in determining postoperative complications, emphasizing the importance of meticulous bloodless dissection even where this requires prolonged operative procedures. The authors followed Japanese practice in leaving large drains in the left subphrenic space for about 7 days after operation. Japanese doctrine attributes great importance to the appropriate use of drains in reducing the frequency and seriousness of peripancreatic sepsis (M. Sasako, personal communication). Mortality following anastomotic leakage or pancreatic fistula was one of six patients, which is relatively satisfactory, but there are no comparative data to allow objective assessment of the importance of this practice. Excellent postoperative monitoring facilities in an ICU or surgical high dependency unit are necessary for this kind of surgery and, like many other British surgeons, the authors regularly experience problems in gaining access to these resources. Changes in staffing and training in the UK have meant that a senior trainee is often not available to assist in or be trained in this procedure. When the only assistance is a very junior trainee, the course of the D_2 operation is considerably slower and more troublesome, and subjectively much more stressful. It would be surprising if the risks of complications were not increased in the absence of adequate assistance, and the influence of this factor on the present results is currently being analysed.

In conclusion, this study shows an apparent learning curve for D_2 gastrectomy over 18–24 months or 15 to 25 cases. There was a significant decrease in postoperative morbidity during this time, and mortality decreased from two of ten patients in the first year to none of 11 in the third year of experience. Reduced endeavour appeared to play little part in this improvement, but more cautious case selection and improved operative tactics and skill seem likely to have played a major role. These findings add weight to the argument that D_2 resection should be practised only in centres where adequate training and experience is available.

Acknowledgements

The authors thank Professor Mitsuru Sasako, National Cancer Center Hospital, Tokyo, Mr David Kerrigan, Consultant Surgeon, Fazakerley Hospital, Liverpool, and Mr Graham Copeland, Consultant Surgeon, Warrington General Hospital, for helpful criticism and discussion.

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British Journal of Surgery 1996, 83, 1599

Case report

Double Y–V plasty for postsurgical anal stricture

B. NEELAKANDAN

Raja Muthia Medical College, Annamalai University,
Chidambaram 608 001, Tamil Nadu, India
Correspondence to. Mr B. Neelakandan

Anal stricture is one of the late complications of haemorrhoidectomy, and occurs particularly when the perianal skin has been widely excised. Many patients respond to an initial trial of daily regular dilatation with anal dilators. In some, this conservative treatment is not effective and surgical correction is warranted. This paper reports successful anoplasty using a double Y–V plasty in two such patients.

Case report

Two men aged 38 and 45 years presented with intractable constipation of 2 years' duration. Both had undergone haemorrhoidectomy elsewhere 3–4 years before presentation. Their initial postoperative course had been uneventful. Examination in both revealed a dense stricture of the anal canal, not allowing even the tip of the little finger to be admitted. Both had an unsuccessful trial of dilatation with anal dilators. Both were free from any other disorder.

Under epidural anaesthesia, anoplasty was peformed in these two patients. Y-shaped incisions were made on either side of the anal canal with the stem of the Y incision starting within the anal canal cutting open the fibrotic ring of tissue, taking care not to injure any sphincter muscle. Two triangular flaps were then raised, advanced into the anal canal and sutured with 3/0 polyglactin (both subcutaneous and subcuticular), thus creating two V-shaped sutured wounds. After operation liquid diet and codeine sulphate were given to the patients and defaecation was avoided for 4 days. Both patients had satisfactory postoperative results with follow-up for 2·5 and 4 years. Both were free from constipation with normal continence. They received anal dilatation every week for the first 2 months after operation and monthly thereafter. They were taught daily self-dilatation.

Discussion

When conservative methods of anal dilatation fail in patients with anal stricture following haemorrhoidectomy, surgical options for anal reconstruction are sought[1]. There are many methods of anal reconstructive surgery including the rhomboid flap, Y–V plasty, V–Y plasty[2–5], and island flap techniques. The technique of double Y–V plasty, using tissue from either side of the anal canal, was a useful and effective technique for the two patients reported here.

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Paper accepted 17 January 1996

British Journal of Surgery 1996, 83, 1600–1603

Prognostic significance of lymph node metastasis in advanced carcinoma of the stomach

S. J. KWON and G. S. KIM

Department of Surgery, School of Medicine, Hanyang University, Seoul, Korea
Correspondence to: Dr S J. Kwon, Department of General Surgery, Hanyang University Hospital, 17 Haengdang-Dong, Sungdong-Ku, Seoul 133-792, Korea

This study attempted to clarify the prognostic factors in advanced gastric cancer, with special reference to lymph node metastasis. It was a retrospective study of 401 patients with stage III and IV gastric cancer operated on during the 5 years from 1988 to 1993. A significant relationship was found between the 5-year survival rate and (1) the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes (ratios of 1–15, 16–30 and 31 per cent or more were associated with a 5-year survival rate of 81, 23 and 17 per cent respectively), (2) stage N_1 or N_2 of the Union Internacional Contra la Cancrum tumour node metastasis classification (58 and 27 per cent respectively) and (3) the number of metastatic lymph nodes (1–3, 4–7 and 8 or more were associated with a 5-year survival rate of 67, 49 and 32 per cent respectively). Multivariate survival analysis using Cox's proportional hazard model was applied to these three forms of lymph node status. Among these three variables, the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes was the most meaningful prognostic factor.

In Korea, stomach cancer was the most prevalent cancer in men (28·3 per cent) and the second most common cancer in women (17·9 per cent) in 1992. Over 50 per cent of patients with gastric cancer operated on in Korea have stage III or IV disease, and a poor prognosis. This study was designed to determine the most useful prognostic factor with respect to lymph node status.

Patients and methods

Between 1988 and 1993, 401 patients with advanced gastric cancer (stage III, 308; stage IV, 93) underwent operation. This represents 54 per cent of the total of 739 patients with primary gastric adenocarcinoma who underwent operation in the unit over the same period. Histopathological examination was carried out to determine the depth of cancer invasion, histological type and presence of metastatic lymph nodes.

The macroscopic classification (Borrmann type), tumour location, number of metastatic lymph nodes, ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes, age and sex of patients were also evaluated. The tumour location was divided into upper, middle and lower third of the stomach, and when the tumour extended to more than two sections it was classified as diffuse. The extent of residual tumour was classified as R_0 (no residual tumour), R_1 (microscopic residual tumour) and R_2 (macroscopic residual tumour).

In patients who underwent curative resection (classified as R_0, $n = 301$), lymph node status was studied. Patients were classified according to the Union Internacional Contra la Cancrum (UICC) tumour node metastasis (TNM) staging categories and were divided into two groups, N_1 and N_2. The patients were divided into three groups according to the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes: 15 per cent or less, 16–30 per cent, and 31 per cent or more. They were also divided into three groups according to the number of metastatic lymph nodes: 1–3, 4–7, and 8 or more.

Follow-up information was obtained by routine clinical appointments or telephone contact with the patients or their family. Examination of the upper gastrointestinal tract, by means of endoscopy and ultrasonography, was performed at 6-monthly or 1-year intervals to detect cancer recurrence. If symptoms or physical signs suggestive of recurrence developed, or if serum levels of tumour markers were raised, patients were investigated by computed tomography or chest radiography in addition. The mean follow-up period was 18·3 (range 1–67) months.

Cumulative survival rates were calculated with the Kaplan–Meier method and compared with the log rank test. Deaths from unrelated causes were censored. The Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA) for Windows program was used for simultaneous multivariate adjustment of all covariates by Cox regression analysis. $P < 0.05$ was considered statistically significant.

Results

Study population and general tumour characteristics

The median age of patients was 55 (range 27–83) years. The male : female ratio was 1·8 : 1 (*Table 1*). The tumour site was most frequently in the lower third. Three-quarters of tumours were Borrmann type III and most of the remainder were type IV. The most frequent histological type was poorly differentiated tubular adenocarcinoma (*Table 1*).

Morbidity and mortality

There were four deaths in the first 30 days after operation, three following palliative surgery (one from tumour bleeding and two from metastasis). One patient died after curative surgery (duodenal stump leakage).

The major postoperative complications were bleeding (four after curative surgery), anastomotic leakage (one after curative surgery, one after non-curative operation) and intestinal obstruction (one after curative surgery).

Lymph node status

Curative resection was attempted in 319 patients, but in only 301 cases was there pathological confirmation of curative resection (classified as R_0). In these 301 patients,

Presented in part to the 14th World Congress on the Collegium Internationale Chirurgiae Digestivae in Los Angeles, California, USA, September 1994
Paper accepted 7 January 1996

Table 1 Details of patients and tumours

Median (range) age (years)	55 (27–83)
Sex ratio (M:F)	256:145
UICC stage	
IIIa	177 (44)
IIIb	131 (33)
IV	93 (23)
Tumour location	
Upper third	48 (12)
Mid third	95 (24)
Lower third	221 (55)
Diffuse	37 (9)
Borrmann type	
I	3 (1)
II	32 (8)
III	308 (77)
IV	58 (14)
Histological classification (WHO)	
Papillary adenocarcinoma	6 (1)
Tubular adenocarcinoma	
Well differentiated	7 (2)
Moderately differentiated	112 (28)
Poorly differentiated	159 (40)
Signet ring cell carcinoma	110 (27)
Mucinous adenocarcinoma	7 (2)
Type of operation	
Curative resection (UICC R_0)	
Total gastrectomy	77 (19)
Subtotal gastrectomy	224 (56)
Palliative resection (UICC R_1 or R_2)	
Total gastrectomy	19 (5)
Subtotal gastrectomy	65 (16)
Bypass surgery	16 (4)

Values in parentheses are percentages. UICC, Union Internacional Contra la Cancrum; WHO, World Health Organization

the total number of dissected lymph nodes was 10 706 (mean 35·6, range 14–114) and the total number of metastatic lymph nodes was 3099 (mean 10·3, range 1–56).

The 5-year survival rate of 164 patients with stage N_1 disease and 137 with N_2 were 58 and 27 per cent ($P = 0\cdot0001$) (*Fig. 1*). The 5-year survival rate of 126 patients with fewer than 15 per cent metastatic lymph nodes of the total number of dissected nodes was 81 per cent; in 84 with 16–30 per cent it was 23 per cent; and in 91 with 31 per cent or more involved nodes it was 17 per cent ($P < 0\cdot0001$) (*Fig. 2*). The 5-year survival rate of 78 patients with 1–3 involved lymph nodes was 79 per cent, in 60 with 4–7 involved nodes it was 49 per cent and in 163 with 8 or more involved nodes it was 32 per cent ($P = 0\cdot008$) (*Fig. 3*).

The number of metastatic lymph nodes within each stage (IIIa and IIIb) did not significantly affect mean survival times but the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes in stage IIIa and IIIb showed a significant relationship with mean survival times (*Table 2*).

Multivariate analysis using the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes, N_1 and N_2 in the UICC TNM staging categories, and the number of metastatic lymph nodes related to survival in the 301 patients who underwent curative (R_0) resection, showed the relative risk of death as 2·4294, 2·1150 and, 0·6722 respectively (*Table 3*). Significant correlation was found between the relative risk

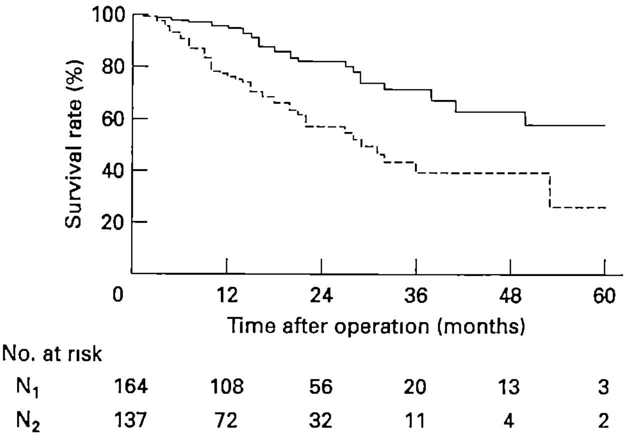

Fig. 1 Survival of patients with respect to stages N_1 (———) and N_2 (– – –) in the Union Internacional Contra la Cancrum tumour node metastasis classification. $P < 0\cdot0001$ (log rank test)

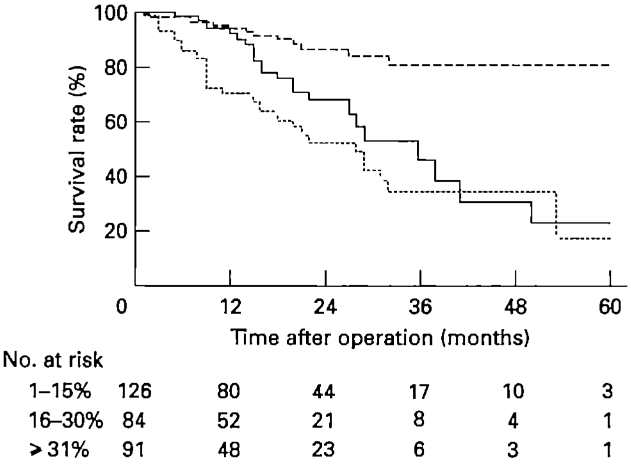

Fig. 2 Survival according to the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes. – – – –, 1–15 per cent; ———, 16–30 per cent, ------, 31 per cent or more. $P < 0\cdot0001$ (log rank test)

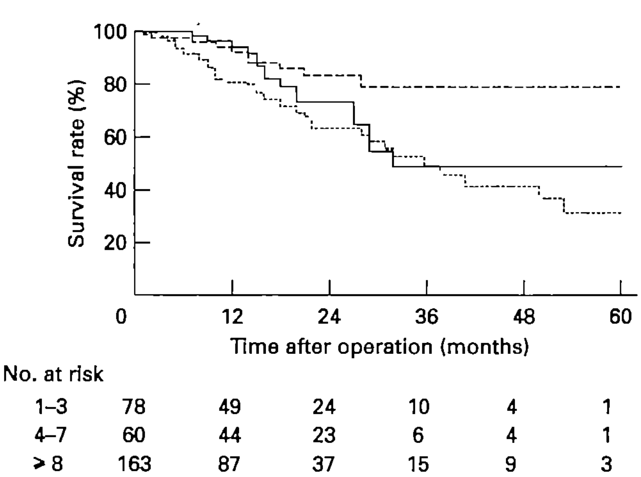

Fig. 3 Survival according to the number of metastatic lymph nodes. – – – –, 1–3 nodes; ———, 4–7; -----, 8 or more. $P = 0\cdot008$ (log rank test)

Table 2 Length of survival related to lymph node status following curative resection

	Stage IIIa		Stage IIIb	
	Survival (months)*	*n*	Survival (months)*	*n*
No. of no. of metastatic lymph nodes				
1–3	51 (44–57)	65	42 (32–52)	13
4–7	47 (38–55)	36	32 (22–42)	20
≥8	44 (38–51)	66	31 (25–38)	81
P†	0·4503		0·2707	
Ratio of no. of metastatic lymph nodes to total no. of dissected lymph nodes (%)				
1–15	53 (49–58)	94	44 (38–50)	29
16–30	43 (33–53)	44	34 (22–46)	34
≥31	36 (29–43)	29	26 (20–33)	51
P†	0·0098		0·0029	

*Values are mean (95 per cent confidence interval). †Log rank test

Table 3 Cox regression analysis for patients with advanced gastric cancer by lymph node status (after curative resecton)

Prognostic variable	β coefficient	s.e.m.	Relative risk of death (exponential coefficient)	*P*
Ratio of no. of metastatic lymph nodes to total no. of dissected lymph nodes (1–15, 16–30, ≥31%)	0·8876	0·2220	2·4294	0·0001
N_1 and N_2 in UICC TNM classification (N_1, N_2)	0·7490	0·2655	2·1150	0·0048
No. of metastatic lymph nodes (1–3, 4–7, ≥8)	− 0·3972	0·2480	0·6722	0·1092

UICC, Union Internacional Contra la Cancrum; TNM, tumour node metastasis

of death and the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes. Simultaneous multivariate adjustment of the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes, Borrmann type, N_1 or N_2 in the UICC TNM staging (N), distant metastasis (M), age, depth of invasion (T), extent of operation, histological type, tumour location, sex, number of metastatic lymph nodes and adjuvant chemotherapy by Cox regression analysis showed that the three most important prognostic factors were the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes, the macroscopic appearance (Borrmann type) and the N_1 and N_2 stage in the UICC TNM classification.

Discussion

The prognosis of patients with gastric cancer is related to numerous variables. It is not easy to identify the most important variables with regard to prognosis, because they are interrelated. To determine the most important factors 401 patients with primary gastric adenocarcinoma treated in 5 years between 1988 and 1993 were studied.

Using the data of the Surveillance, Epidemiology and End Results series, Curtis and Kennedy[1] analysed 11 variables: age, sex, race, depth of invasion, lymph node metastasis, distant metastasis, location, histological type, grade of differentiation, localized or diffuse growth, and type of extension to adjacent tissue. They proposed a staging system based on three important variables: depth of invasion, lymph node metastasis and distant metastasis. The Japanese Research Society for Gastric Cancer (JRSGC) demonstrated by multivariate analysis of 4946 cases that the important prognostic factors of gastric cancer were the depth of invasion and lymph node metastasis[2]. Shiu *et al.*[3] performed multivariate regression analysis on 210 patients with gastric cancer who underwent curative resection and identified as poor prognostic factors non-pyloric cancer, more than three lymph node metastases, microscopic tumour invasion at the resection margin, incomplete lymph node dissection and total gastrectomy. In the present study the 5-year survival rate of patients with Borrmann type IV disease was significantly worse (zero) than that of those with type III lesions (54 per cent) ($P<0·0001$), and the 5-year survival rate of patients with stage N_1 disease was significantly better than that of those with N_2 ($P<0·0001$).

Cady *et al.*[4] reported a significant difference in survival when patients were grouped according to the number of metastatic lymph nodes into three groups of zero, one to three, and four or more. Okusa *et al.*[5] also reported differences in the 5-year survival rates of 81, 63, 47 and 27 per cent when the numbers of metastatic lymph nodes were grouped as zero, one to three, four to six, and seven or more. They also reported that, when the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes was divided as 0, 1–25, 26–50 and over 50 per cent, 5-year survival rates were 86, 66, 30 and 23 per cent respectively. According to this result, these authors proposed that the survival rate decreases as the number and ratio of metastatic lymph nodes increase. The present study has shown a similar effect when patients were divided into three groups according to the number and ratio of metastatic lymph nodes. Soga *et al.*[6] reported that, when the number of dissected lymph nodes was more than 30, 5-year survival rates were better than when it was less than 30, and proposed wide lymph node dissection to achieve better results. In contrast, the present authors found no effect on survival when the number of dissected lymph nodes was more than 30.

This study has confirmed earlier observations[7,8] of a clear effect of UICC TNM stage on the 5-year survival rate. However, there are some problems with the lymph node status of the UICC TNM classification. Exact measurement of the distance between the margin of the tumour and each lymph node cannot be made in a three-dimensional body structure. Especially in an *en bloc* dissected specimen, identification of N_1 and N_2 according to the UICC TNM classification is difficult. For these reasons, the ratio of the number of metastatic lymph nodes to the number of dissected lymph nodes is recommended as the most reliable prognostic factor in estimating the survival of patients with gastric cancer.

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British Journal of Surgery 1996, 83, 1604–1607

Prognostic significance of lymph node dissection in gastric cancer

G. DE MANZONI, G. VERLATO*, A. GUGLIELMI, E. LATERZA,
M. GENNA and C. CORDIANO

*First Department of General Surgery and *Department of Medical Statistics, University of Verona, Verona, Italy*
Correspondence to: Dr G. de Manzoni, First Department of General Surgery, Borgo Trento Hospital, Piazza Stefani 1, 37 126 Verona, Italy

The results for 162 patients who underwent curative gastrectomy for gastric cancer from January 1988 to June 1994 were analysed statistically with special reference to the effect of lymph node dissection. Median survival was 69·3 months and the overall cumulative 5-year survival rate was 50·2 (95 per cent confidence interval (c.i.) 41·6–58·1) per cent. By univariate analysis age, histology, depth of tumour invasion, node involvement, number of metastatic lymph nodes and type of lymphadenectomy were found to be significant factors related to survival time. Multivariate analysis with the Cox model and stratified for tumour node metastasis stage revealed that only the number of metastatic nodes ($P = 0{\cdot}04$) and the extent of lymphadenectomy ($P = 0{\cdot}003$) affected survival independently. With respect to D_1 lymphadenectomy, the relative risk associated with D_2 and D_4 lymphadenectomy was respectively 0·61 (95 per cent c.i. 0·34–1·10) and 0·26 (95 per cent c.i. 0·12–0·60). The 5-year survival rate was 28 per cent for patients who had a D_1 dissection, 63 per cent for those who had D_2 and 68 per cent for those who had D_4. These results suggest that extended lymphadenectomy (D_2) and especially superextended lymphadenectomy (D_4) can improve survival in patients with gastric cancer.

In Japan the reduction in mortality from gastric cancer in recent years has exceeded the decrease in incidence, and the cure rate is superior to that achieved in Western countries[1].

Japanese surgeons attribute the improvement in prognosis both to the increased detection rate of early gastric cancer and to the introduction of extended lymphadenectomy[2,3], but the majority of Western surgeons oppose such aggressive surgery because of the small survival advantage and high mortality and morbidity rate[4,5].

To estimate the role of lymph node dissection, a prospectively documented study with multivariate analysis was performed in patients who had potentially curative resection for gastric carcinoma.

Patients and methods

Between 1 January 1988 and 15 June 1994, 223 patients with histologically proved primary gastric carcinoma underwent surgical treatment in the First Department of General Surgery, University of Verona. Some 36 patients had only exploratory laparotomy or a palliative bypass procedure, and 187 underwent gastric resection (resectability rate 83·9 per cent). Of these, 162 (86·6 per cent) who underwent potentially curative resection with complete macroscopic and microscopic removal of the tumour were included in the study.

The mean(s.d.) age of the patients was 64·6(11·7) years; the ratio of men to women was about 2 to 1 (111 men). Patients were followed prospectively in the outpatient clinic, which they attended regularly at least once every 4 months.

Tumours were staged according to the pathological tumour node metastasis (pTNM) classification of the Union Internacional Contra la Cancrum and histological classification followed the criteria of Lauren.

Lymph node dissection was classified according to Japanese Research Society for Gastric Cancer rules[6]: D_1 lymphadenectomy (resection of perigastric nodes in positions 1–6), D_2 lymphadenectomy (resection of nodes in positions 1–11) and D_4 lymphadenectomy (resection extended to the nodes in positions 12–16). The choice of surgical procedure has been explained in detail elsewhere[7]; briefly, it was based on the site and depth of tumour invasion, assessed by preoperative endoscopic ultrasonography and intraoperative *in vitro* ultrasonography performed on the resected specimen. Generally, patients with the more advanced stages (T_2, T_3 and T_4) underwent extended or superextended lymphadenectomy.

None of the patients received postoperative chemotherapy or radiotherapy.

Statistical analysis

Survival data included postoperative deaths, while deaths from causes other than gastric cancer were considered as censored observations at the time of death. No patient was lost to follow-up. The results are presented as 5-year survival rates with 95 per cent confidence intervals (c.i.).

The probability of survival was calculated for different subgroups according to the Kaplan–Meier method[8] and different survival curves were compared with the log rank test. Cox's regression model[9] was used to evaluate the prognostic significance of six selected factors: age, sex, tumour location (fundus, corpus and antrum), histological type (intestinal, diffuse), type of lymphadenectomy and number of metastatic lymph nodes. The number of metastatic nodes was coded as a four-level variable: no node metastases; metastases in one to three nodes; metastases in four to seven nodes; and metastases

Table 1 Postoperative morbidity and mortality according to the extent of lymph node dissection

	D_1 ($n = 65$)	D_2 ($n = 59$)	D_4 ($n = 38$)
Death	4 (6)	2 (3)	1 (3)
Complications			
Wound infection	2	2	2
Intra-abdominal abscess	1	2	2
Anastomotic leakage	1	3	0
Duodenal stump leakage	1	0	0
Pancreatic fistula	1	2	3
Necrotizing pancreatitis	1	0	0
Haemorrhage	2	1	0
Cardiopulmonary	3	3	5
Other	0	1	0
Total	12 (18)	14 (24)	12 (32)

Values in parentheses are percentages

Paper accepted 17 January 1996

in more than seven nodes. Each prognostic factor was analysed before and after adjustment for all other variables. The analysis was carried out after stratifying for TNM stage (Ia, Ib, II, IIIa, IIIb, IV), which could not be included into the Cox model because it presented a significant interaction with time, according to the goodness-of-fit test. The relative risk for the continuous variable (age) was calculated on the basis of an increase in the value of one standard deviation.

Table 2 Relationship between number of nodes dissected and number of metastatic nodes according to the degree of node dissection

Type of lymphadenectomy	No. of dissected lymph nodes*	No. of metastatic lymph nodes*	Ratio of metastatic: dissected lymph nodes (%)
D_1	18·2(10·6)	6·6(6·0)	34·5
D_2	31·3(13·3)	5·9(8·8)	19·0
D_4	47·0(16·6)	6·6(7·5)	14·1

*Values are mean(s.d.)

Table 3 Univariate analysis of eight clinical and pathological variables related to 5-year survival calculated by the Kaplan–Meier method in patients with gastric cancer after curative resection

Variable	No of patients*	5-year survival rate (%)†	P‡
Sex			
M	111 (68·5)	46 (36–56)	0·16
F	51 (31·5)	60 (44–73)	
Age (years)			
≤60	53 (32·7)	69 (54–80)	0·01
61–70	55 (34·0)	41 (27–55)	
>70	54 (33·3)	41 (27–55)	
Histology			
Intestinal	76 (46·9)	60 (47–71)	0·007
Diffuse	86 (53·1)	41 (30–52)	
Location			
Upper third	50 (30·9)	35 (21–50)	0 24
Middle third	48 (29·6)	60 (45–72)	
Lower third	64 (39·5)	54 (41–66)	
Lymph node dissection			
D_1	65 (40·1)	28 (18–40)	<0·001
D_2	59 (36·4)	63 (48–75)	
D_4	38 (23·5)	68 (48–81)	
No. of nodes			
0	51 (31·5)	92 (80–97)	<0 001
1–3	27 (16·7)	64 (38–81)	
4–7	31 (19·1)	33 (16–50)	
>7	53 (32 7)	15 (6–26)	
Depth of invasion			
T_1	42 (25·9)	88 (68–96)	<0·001
T_2	24 (14·8)	90 (67–98)	
T_3	74 (45·7)	31 (20–42)	
T_4	22 (13·6)	7 (1–24)	
Nodal involvement			
N_0	50 (30·9)	94 (82–98)	<0·001
N_1	56 (34·6)	42 (29–55)	
N_2	56 (34·6)	21 (11–34)	

Values in parentheses are *percentages and †95 per cent confidence intervals. ‡Log rank test

Results

Seven patients died within the first 30 postoperative days (operative mortality rate 4·3 per cent) and 38 patients (23·5 per cent) developed postoperative general and surgical complications. Morbidity and mortality after different extent of node dissection are shown in *Table 1.*

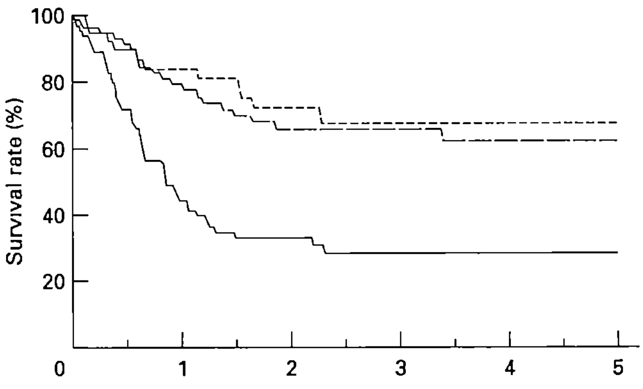
The median follow-up for surviving patients was 37·7 (range 10·6–111·4) months.

The overall number of excised lymph nodes was 4851, yielding a mean(s.d.) 29·9(17·0) lymph nodes per patient.

Table 4 Relative risk of death from gastric cancer after stratifying for stage, before and after adjusting for all other variables

	Relative risk* stratified for stage		
Variable	No adjustment	Adjusted for all other variables	P†
Sex (F *versus* M)	0·90 (0·53–1·52)	1 07 (0·58–1·97)	0·83
Age (s.d. 11·7 years)	1·45 (1·09–1·92)	1·24 (0·90–1·70)	0·18
Site			
Corpus *versus* fundus	1·04 (0·56–1·92)	0·86 (0·45–1·66)	0·90
Antrum *versus* fundus	0·92 (0·54–1·56)	0·91 (0·51–1·63)	
Histology (diffuse *versus* intestinal	1·77 (1·07–2·92)	1·38 (0·79–2·41)	0 26
Lymphadenectomy			
D_2 *versus* D_1	0·64 (0·37–1·10)	0 61 (0·34–1·10)	0·003
D_4 *versus* D_1	0·25 (0·12–0·52)	0 26 (0·12–0·60)	
D_1 *versus* D_2	1·57 (0·90–2·72)	1·64 (0·91–2·94)	0·003
D_4 *versus* D_2	0·40 (0·18–0·87)	0·44 (0·19–1 01)	
Metastatic nodes			
1–3 *versus* 0	0·73 (0·16–3·30)	1·04 (0·23–4·76)	0·04
4–7 *versus* 0	1·36 (0·31–6·04)	2·13 (0·46–9 97)	
>7 *versus* 0	2·10 (0·48–9·26)	3·38 (0·73–15 62)	

Values in parentheses are 95 per cent confidence intervals. *Relative risk derived from Cox regression analysis, calculation of the relative risk for continuous variables was based on an increase in the value of one standard deviation; †multivariate analysis



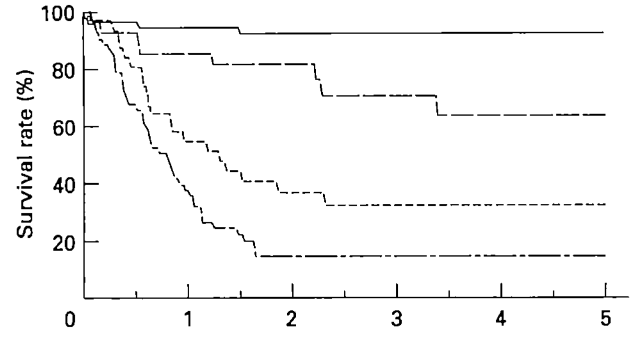
No. at risk										
D_1	65	47	28	17	16	12	11	10	9	6
D_2	59	53	44	35	31	24	24	19	16	11
D_4	38	34	32	27	16	13	12	9	6	4

Fig. 1 Kaplan–Meier curves of patient survival according to the extent of lymphadenectomy: ——, D_1; —–, D_2; ---, D_4

Table 5 Relative risk of death as a function of lymphadenectomy and node involvement

Lymphadenectomy	N_0 and N_1*	N_2
D_1	1·0	1·0
D_2	0·42 (0·16–1·08)	0·56 (0·27–1·15)
D_4	0·10 (0·01–0·78)	0·42 (0·18–0·95)

Values in parentheses are 95 per cent confidence intervals. *Owing to the small number of failures in N_0, lymph node involvement had to be recoded as a two-level variable in multivariate analysis (N_0 and N_1 *versus* N_2)



No. at risk										
0	51	49	45	41	33	26	24	19	15	7
1–3	27	25	23	18	16	12	12	9	6	4
4–7	31	25	17	11	9	7	7	6	6	6
>7	53	35	19	9	5	4	4	4	4	4

Fig. 2 Kaplan–Meier curves of patient survival according to the number of nodes showing metastatic carcinoma: ——, no positive nodes; — — —, one to three positive nodes; - - -, four to seven positive nodes; - - - - - - -, more than seven positive nodes

Metastatic lymph nodes amounted to 6·2(7·4) per patient, corresponding to 20·9 per cent of all excised lymph nodes. Details of the number of dissected and metastatic nodes for each type of lymphadenectomy are given in *Table 2*.

The median survival time was 69·3 months and the overall cumulative 5-year survival rate was 50·2 (95 per cent c.i. 41·6–58·1) per cent.

The depth of tumour invasion and nodal involvement significantly influenced 5-year survival (*Table 3*). The effect of these two fundamental prognostic factors was not stable over time, as patients with N_0 and T_1 disease experienced the highest postoperative mortality rate but also the highest 5-year survival rate. Because the Cox model assumes that the risk ratio remains constant over time, subsequent analysis was carried out stratifying for TNM stage. After stratification, age, histology, number of metastatic lymph nodes and type of lymphadenectomy were significant factors related to length of survival. After adjusting for age, sex and other risk factors, only the number of metastatic nodes ($P = 0{\cdot}04$) and the type of lymphadenectomy ($P = 0{\cdot}003$) independently affected survival (*Table 4*). When tumour stage was not considered, survival curves for D_2 and D_4 dissection were superimposed (*Fig. 1*) and the corresponding 5-year survival rates were similar (63 and 68 per cent respectively) (*Table 3*). After stratifying for stage, a significant difference between D_2 and D_4 emerged, and D_4 appeared to be associated with improved survival (relative risk for D_4 *versus* $D_2 = 0{\cdot}40$ (95 per cent c.i. 0·18–0·87), $P = 0{\cdot}02$). This difference narrowed slightly and after taking into account all other variables it failed to reach significance ($P = 0{\cdot}053$) (*Table 4*).

The impact on survival of superextended lymphadenectomy seemed to be greater for N_0 and N_1 tumours than for N_2 lesions (*Table 5*); however, this trend was not significant, perhaps because of the small number of patients.

Postoperative survival curves related to the number of metastatic nodes are shown in *Fig. 2*.

Discussion

The therapeutic value of extended lymphadenectomy in the surgical treatment of gastric cancer is still controversial. Several Japanese authors[2,3,10] have reported better long-term results after extensive lymphadenectomy (D_2) compared with a limited procedure (D_1). Some institutes in Western countries have also described benefit from D_2 dissection, particularly in advanced stages of the disease[11–13].

In the present study multivariate analysis identified lymphadenectomy, together with depth of tumour invasion and node involvement, as the strongest independent prognostic factors for survival, and more favourable prognosis was obtained with the extension of the node dissection. Patients who underwent D_4 dissection presented a lower risk of death from gastric cancer, compared with those who underwent D_1 ($P = 0{\cdot}001$) or D_2 ($P = 0{\cdot}05$) dissection, although the difference between extended (D_2) and superextended (D_4) lymphadenectomy requires further confirmation.

The role of the superextended node dissection has been studied only in some limited Japanese series that showed a survival advantage in the advanced stages (IIIa, IIIb, IVa) in spite of increased postoperative morbidity and mortality rates[14,15], but its indications have not yet been defined.

In this paper the first Western experience is presented in which the prognostic value of D_4 dissection has been evaluated. From these preliminary results D_4 shows a survival advantage and its impact tends to be greater, although not significantly so, in patients with no or limited (N_1) nodal disease. The concept that lymphadenectomy is beneficial only when it encompasses the disease widely is not new[9], and is probably due to the presence of cancer cells in the regional nodes even in cases classified as pN_0[16,17].

Data published recently from the Dutch prospective randomized trial[5] comparing D_2 and D_1 dissection showed a significant increase in postoperative morbidity and mortality rates in patients having D_2 dissection. In the present study, as well as in the German gastric carcinoma study[12], no differences were observed in the 30-day mortality rate between D_1, D_2 and D_4 dissection, with only a slightly higher complication rate for D_4. All extensive node dissections in the present investigation were performed by the same senior surgeon (C.C.) and this could explain the low rate of surgical complications after extended operation.

Univariate as well as multivariate analysis showed that the number of metastatic nodes also plays an important role, although less than the effect of lymphadenectomy, in the long-term results after curative resection. In particular, a remarkable decrease in survival was recorded when there were more than three metastatic nodes. These findings are similar to those obtained in previous studies[18,19] and suggest that the number of metastatic nodes is an important prognostic factor in patients with gastric cancer, with a cut-off number of three. For this reason, numbers of involved nodes should be taken into account in the nodal stage classification, based at present only on sites.

In conclusion, while awaiting the results of the prospective randomized trials currently under way in Europe[20,21], these data show a significantly favourable effect of wide lymphadenectomy, which is not associated with an increase in postoperative mortality rate. The impact on survival of D_4 dissection seems to be greater, but further studies involving a larger number of patients are needed to verify this finding.

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British Journal of Surgery 1996, 83, 1608–1614

Decreased E-cadherin expression is associated with haematogenous recurrence and poor prognosis in patients with squamous cell carcinoma of the oesophagus

S. TAMURA, H. SHIOZAKI, M. MIYATA, T. KADOWAKI, M. INOUE, S. MATSUI, T. IWAZAWA, T. TAKAYAMA, M. TAKEICHI* and M. MONDEN

*Department of Surgery II, Osaka University Medical School, Osaka and *Department of Biophysics, Faculty of Science, Kyoto University, Kyoto, Japan*

Correspondence to: Dr S. Tamura, Department of Surgery II, Osaka University Medical School, 2-2 Yamadaoka, Suita, Osaka 565, Japan

Reduced expression of E-cadherin is associated with tumour invasiveness and metastasis. To elucidate whether E-cadherin expression correlates with clinical outcome in patients with oesophageal cancer, 62 patients were investigated immunohistochemically using an anti-E-cadherin monoclonal antibody (HECD-1). Eight patients had normal levels of expression in the tumour, 25 had tumours that expressed high levels (50 per cent or more tumour cells staining positive for E-cadherin) and 29 had tumours expressing low levels (less than 50 per cent of cells expressing E-cadherin). Patients with normally expressing tumours had a better prognosis at 3 years than those with low-expressing tumours ($P<0{\cdot}05$). Postoperative death was correlated significantly with lymphatic invasion, lymph node metastasis, E-cadherin expression and depth of invasion ($P<0{\cdot}05$). Furthermore, haematogenous recurrence was correlated with E-cadherin expression ($r_S=0{\cdot}38$, $P<0{\cdot}01$) and blood vessel invasion ($r_S=0{\cdot}28$, $P<0{\cdot}05$). These results suggest that evaluation of E-cadherin immunoreactivity may predict haematogenous recurrence and poor prognosis in patients with oesophageal cancer.

Oesophageal carcinoma is generally considered an extremely aggressive carcinoma with a poor prognosis[1]. The majority of patients have already advanced tumours and lymph node metastases at the time of diagnosis[2]. Clinicopathological factors related to the prognosis of oesophageal cancer include lymph node status[3–5], depth of invasion[5], tumour length[6] and presence of residual disease at surgery[5]. More recently, attempts have been made to investigate the relationship between certain molecular markers and the clinical course of squamous cell carcinoma of the oesophagus[7,8].

The initial step in invasion and metastasis is the dissociation of cancer cells from the primary tumour through the breakdown of the cell–cell adhesion system, which consists of at least four families of adhesion molecules (integrin, immunoglobulin, secretin and cadherin families). In particular, the cadherins have been documented as important modulators in this step[9,10].

Cadherins are calcium-dependent cell–cell adhesion transmembrane glycoproteins present on most cells and which mediate homophilic adhesion between cells[9]. E-cadherin, one of the classical cadherins, plays an important role in epithelial integrity[11] and has been detected on the cell surface of normal oesophageal mucosa by immunohistochemical techniques[12]. In other human carcinomas, E-cadherin is frequently reduced or absent in dedifferentiated tumours[12,13], which suggests that it plays a role in the genesis of histological differentiation and may be implicated in the development of invasive properties in human cancer cells. Furthermore, a possible role for E-cadherin as an invasion suppressor molecule has been suggested[9]. However, it is not clear whether reduced E-cadherin immunoreactivity has any prognostic predictive value after surgery in patients with oesophageal cancer.

In this study, the distribution of E-cadherin in squamous cell carcinoma of the oesophagus was compared with histopathological and survival data. E-cadherin expression in oesophageal cancer was also examined for its prognostic value in these patients.

Patients and methods

This study was based on 62 patients with squamous cell carcinoma of the thoracic and abdominal oesophagus who underwent surgical resection between March 1988 and February 1991. No patient had received irradiation or chemotherapy before operation. The series consisted of 57 men and five women of mean(s.e.m.) age 61·1(9·9) (range 34–80) years. Six tumours were in the upper thoracic oesophagus, 45 in the middle thoracic oesophagus and 11 in the lower thoracic or abdominal oesophagus (*Table 1*). Hypopharyngeal tumours, tumours arising in the cervical oesophagus, and adenocarcinomas located at the gastro-oesophageal junction were excluded because of the different behaviour and approach to treatment of these lesions. The operative procedure and postoperative treatment are shown in *Table 2*

Each tumour was cut longitudinally in 5-mm thick sections and one slice of tumour including normal epithelial tissue was used for immunohistochemical staining. The specimen was divided into two or three blocks and embedded in optimal cutting temperature compound (Miles Laboratory, Naperville, Illinois, USA). These fresh specimens were immediately frozen in dry ice acetone and stored at −80°C until stained.

Immunostaining for E-cadherin was performed by the avidin–biotin–peroxidase complex method using the HECD-1 monoclonal antibody as described previously[12]. The sections were counterstained with haematoxylin, dehydrated and mounted.

The expression of E-cadherin on cancer cells was compared with that of normal epithelial cells in the same sample, which always expressed E-cadherin strongly and was used as a positive control (*Fig. 1A*). Negative controls for the expression of E-cadherin were non-epithelial tissues in the same sample, such as muscular tissue and infiltrating lymphocytes. Cancer cells with immunostaining similar to that of normal epithelium were classified as having normal E-cadherin expression (*Fig. 1B*).

Paper accepted 16 January 1996

Table 1 Relationship between E-cadherin immunoreactivity and clinicopathological features

	No. of patients ($n = 62$)	E-cadherin expression Normal ($n = 8$)	E-cad(≥50) ($n = 25$)	E-cad(<50) ($n = 29$)	r_S	P
Sex ratio (M:F)	57:5	5.3	24:1	28:1	−0·27	<0·05
Age (years)						
≤50	7	1	3	3	n.s.	
51–60	20	4	6	10		
61–70	24	1	11	12		
≥71	11	2	5	4		
Location						
Upper thoracic	6	1	2	3	n.s.	
Middle thoracic	45	5	17	23		
Lower thoracic and abdominal	11	2	6	3		
Differentiation grade						
Well	20	6	8	6	0·30	<0·05
Moderate	22	1	10	11		
Poor	20	1	7	12		
TNM classification						
T_1	13	4	7	2	n.s.	
T_2	12	0	4	8		
T_3	30	4	11	15		
T_4	7	0	3	4		
N_0	18	5	8	5	n.s.	
N_1	44	3	17	24		
M_0	60	8	24	28	n.s.	
M_1	2	0	1	1		
Lymphatic invasion						
No	18	6	9	3	0·45	<0·01
Yes	44	2	16	26		
Blood vessel invasion						
No	43	7	18	18	n.s.	
Yes	19	1	7	11		

E-cad(≥50), 50 per cent or more tumour cells staining positive for E-cadherin; E-cad(<50), less than 50 per cent of tumour cells expressing E-cadherin; TNM, tumour node metastasis; n.s., not significant

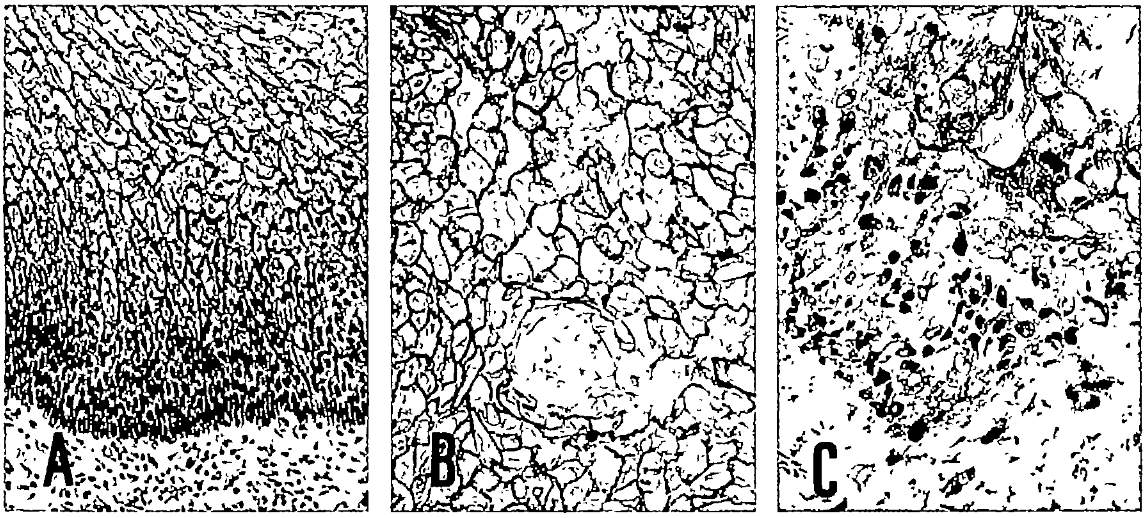

Fig. 1 Immunoreactive E-cadherin expression in human oesophageal carcinoma. A Normal oesophageal epithelium; all epithelial cells express E-cadherin strongly at cell–cell boundaries. B Preserved E-cadherin expression; all tumour cells express E-cadherin strongly. C Reduced E-cadherin expression; this tumour expresses E-cadherin heterogeneously. (Original magnification ×100)

When the tumour was composed of positive but weakly staining or negatively staining areas it was evaluated as having reduced expression of E-cadherin (*Fig. 1C*).

E-cadherin expression was determined by three independent observers who had no knowledge of the histopathological data. The proportion of E-cadherin-positive cells was estimated by comparison with haematoxylin and eosin staining of a consecutive section. When 50 per cent or more of the cancer cells were positive, the tumour was evaluated as E-cad(≥50), and when fewer than 50 per cent stained positive it was evaluated as E-cad(<50). All the observers were in agreement over the E-cadherin expression for samples from all patients with

Table 2 Treatment for oesophageal cancer

	No. of patients ($n = 62$)	Normal E-cadherin ($n = 8$)	E-cad (≥ 50) ($n = 25$)	E-cad (< 50) ($n = 29$)
Operative method				
Blunt dissection	10	1	4	5
Radical oesophagectomy	26	4	13	9
Oesophagectomy with extensive lymph node dissection	25	2	8	15
Other	1	1	0	0
Postoperative treatment				
Radiotherapy				
No	43	8	17	18
Yes	19	0	8	11
Chemotherapy				
No	24	5	8	11
Yes	38	3	17	18

E-cad(≥ 50), 50 per cent or more tumour cells staining positive for E-cadherin; E-cad(< 50), less than 50 per cent of tumour cells expressing E-cadherin

Table 3 Stage of disease according to the Union Internacional Contra la Cancrum classification

Stage	No. of patients ($n = 62$)	Normal E-cadherin ($n = 8$)	E-cad (≥ 50) ($n = 25$)	E-cad (< 50) ($n = 29$)
I	10	4	5	1
IIA	8	1	3	4
IIB	14	0	7	7
III	28	3	9	16
IV	2	0	1	1
Total I and II	32	5	15	12

E-cad(≥ 50), 50 per cent or more tumour cells staining positive for E-cadherin; E-cad(< 50), less than 50 per cent of tumour cells expressing E-cadherin

preserved expression of E-cadherin, and in all but three cases with more than 50 per cent expression of E-cadherin. When there was disagreement between the three observers, the result selected by two observers was defined as the E-cadherin expression.

A consecutive section from each specimen was stained with haematoxylin and eosin for histological evaluation. The clinicopathological classification was based on that of the Union Internacional Contra la Cancrum[14].

The Spearman rank correlation coefficient was used to analyse the correlation between the expression of E-cadherin and clinicopathological data and the influence of clinicopathological factors and E-cadherin expression on haematogenous recurrence and survival. Cumulative survival curves were constructed according to the Kaplan–Meier method, and differences in survival were estimated with the log rank test. Correlation between E-cadherin expression and the frequency of local and/or lymph node recurrence or haematogenous metastasis was assessed with the χ^2 test or Fisher's exact probability test. Statistical significance was defined as $P < 0{\cdot}05$.

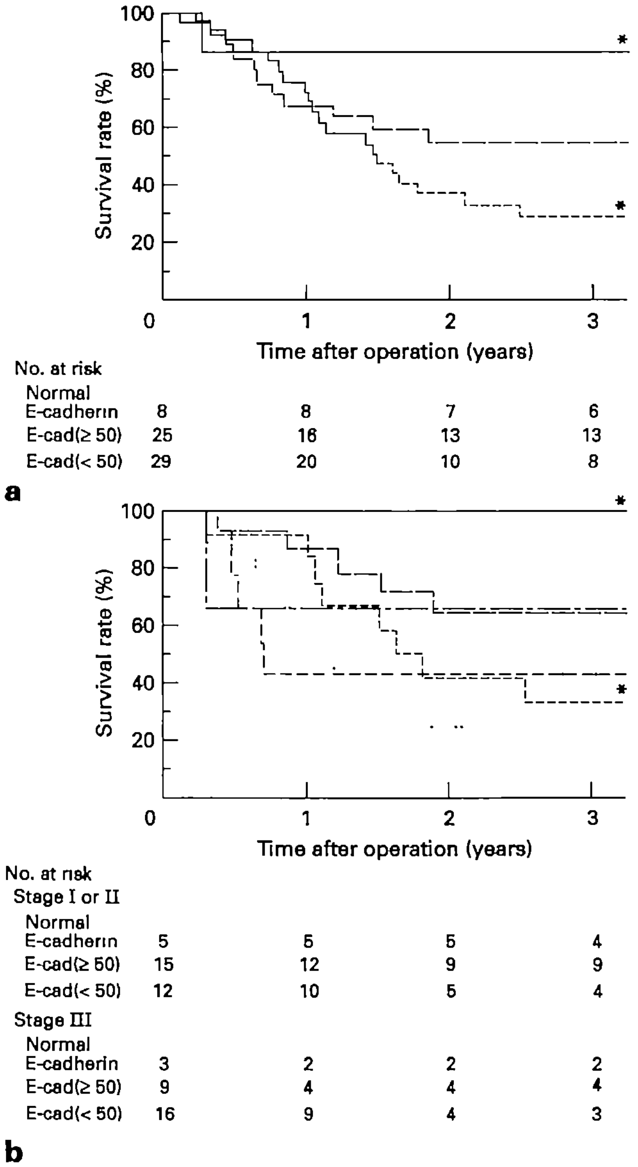

Fig. 2 Kaplan–Meier survival curves according to E-cadherin expression of primary tumour. Deaths unrelated to oesophageal carcinoma were censored at the time of occurrence. E-cad(≥ 50), 50 per cent or more tumour cells staining positive for E-cadherin; E-cad(< 50), less than 50 per cent of tumour cells expressing E-cadherin. **a** Survival curves for 62 patients (———, normal E-cadherin; — — —, E-cad(≥ 50); - - - - -, E-cad(< 50)) show the significant difference between patients with normal E-cadherin-expressing tumours and those with E-cad(< 50) tumours ($^*P < 0{\cdot}05$, log rank test). **b** Survival curves for 32 patients with stage I or II disease (———, normal E-cadherin; — — — —, E-cad(≥ 50); - - - - -, E-cad(< 50)) and 28 with stage III lesions (—·—·—, normal E-cadherin; -·-·-·-, E-cad(≥ 50); ········, E-cad(< 50)) demonstrate the significant difference between patients with normal E-cadherin-expressing tumours and those with E-cad(< 50) tumour in stage I or II ($^*P < 0{\cdot}05$, log rank test) and the non-significant trend to shorter survival of patients with reduced expression of E-cadherin in stage III

Results

E-cadherin expression and clinicopathological factors

Of the 62 primary tumours eight were classified as having normal E-cadherin expression, 25 as E-cad(≥ 50) and 29 as E-cad(< 50). Only two patients had negatively staining tumours and were included in the E-cad(< 50) group.

The relationship between E-cadherin expression and clinicopathological features is shown in *Table 1*. There was a significant difference in sex, differentiation grade and

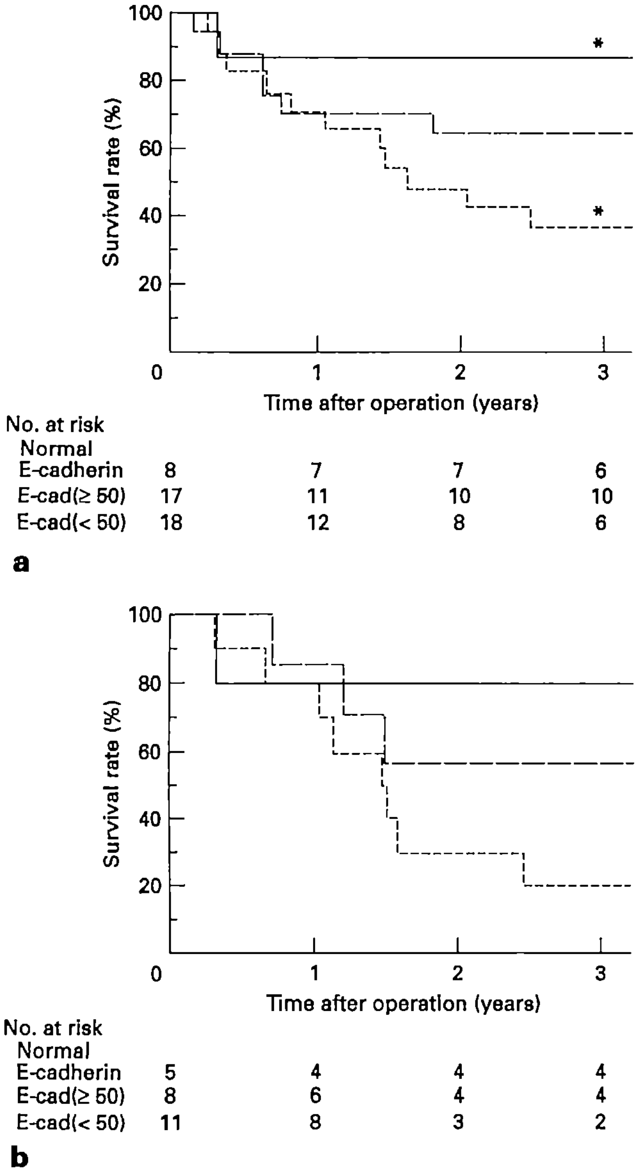

Fig. 3 Survival curves for patients who were not chosen for postoperative radiotherapy (a) or chemotherapy (b). E-cad(≥50), 50 per cent or more tumour cells staining positive for E-cadherin; E-cad(<50), less than 50 per cent of tumour cells expressing E-cadherin ———, normal E-cadherin, - - - -, E-cad(≥50); – – – –, E-cad(<50) $^{*}P<0{\cdot}05$ (E-cad(<50) *versus* normal E-cadherin expression, log rank test) There were no other significant differences

lymphatic invasion between the three groups. No differences were seen in age, location of tumour, tumour node metastasis (TNM) classification or blood vessel invasion.

Although there was a tendency for postoperative radiotherapy and/or chemotherapy to be performed more often in patients with reduced expression of E-cadherin than in those with preserved expression, the difference was not significant (*Table 2*).

E-cadherin expression and survival

Analysis of survival at 3 years after operation shows that reduced E-cadherin expression was strongly correlated with poor prognosis Six of seven patients with normal E-cadherin-expressing tumours, 13 of 24 patients with E-cad(≥50) and eight of 28 patients with E-cad(<50) were alive at 3 years after operation, respectively. There was a statistically significant difference ($P<0{\cdot}05$, log rank test) between patients with normal E-cadherin levels and those with E-cad(<50) tumours. Although patients with E-cad(≥ 50) tumours seemed to have a better prognosis than those with E-cad(<50) lesions, the difference between the survival curves was not significant (*Fig. 2a*). This correlation seemed to persist when survival analysis was performed in the subgroups according to TNM staging (*Table 3*). There was a significant difference between patients with normal E-cadherin-expressing tumours and E-cad(<50) lesions in the analysis of patients with stage I or II tumours ($P<0{\cdot}05$) (*Fig. 2b*). In addition, there was a non-significant trend towards reduced survival for patients with reduced expression of E-cadherin in stage III (*Fig. 2b*).

Table 4 Cause of death: site of recurrence or metastasis

	Normal E-cadherin ($n=8$)	E-cad (≥50)* ($n=25$)	E-cad (<50)* ($n=29$)
Haematogenous metastasis			
Bone	0	0	6 (lung 2, skin 1)
Liver	0	1	3 (lung 1)
Lung	0	1 (bone 1)	1
Local and/or lymph node recurrence			
Peritoneum, lymph node in abdominal cavity	0	1	1
Local, pleura, cervical lymph node	1	8 (skin 1, liver 1)	7
Other			
Pneumonia	0	2 (brain 1, local 1)	2 (local 2)
Hospital death, others	1	0	1
Total	2	13	21

*Values in parentheses indicate the next major site and number of patients. E-cad(≥50), 50 per cent or more tumour cells staining positive for E-cadherin; E-cad(<50), less than 50 per cent of tumour cells expressing E-cadherin

Patients with normal E-cadherin expression had a better prognosis than those with E-cad(<50) tumours, even if they did not receive postoperative radiotherapy (*Fig. 3a*) ($P<0{\cdot}05$) or chemotherapy (*Fig 3b*).

Lymphatic invasion ($r_S=0{\cdot}29$, $P<0{\cdot}05$), N category ($r_S=0{\cdot}27$, $P<0{\cdot}05$), E-cadherin expression ($r_S=0{\cdot}26$, $P<0{\cdot}05$) and T category ($r_S=0{\cdot}26$, $P<0{\cdot}05$) were the significant prognostic variables by Spearman rank correlation.

E-cadherin expression and clinical outcome

Causes of death, divided into three categories (haematogenous metastasis, local and/or lymph node recurrence, and other) are summarized in *Table 4*. Although some patients suffered distant metastases at more than one site, the major metastatic site is shown in *Table 4*, with the second major site in parentheses. At the time of analysis there were 36 deaths among the 62 patients.

In addition, recurrent and/or metastatic disease had occurred in four patients at the time of analysis. Two

Table 5 Relationship between site of recurrence and clinicopathological factors and E-cadherin expression in 60 patients*

	Local and/or lymph node recurrence		Haematogenous recurrence	
	r_S	P†	r_S	P†
TNM classification				
T (primary tumour)	0·38	<0·01	0·03	n.s.
N (regional lymph node)	0·14	n.s.	0·22	n.s
Lymphatic invasion (yes or no)	0·20	n.s.	0·20	n.s
Blood vessel invasion (yes or no)	0·14	n.s.	0·28	<0·05
E-cadherin expression (Normal, E-cad(≥50) or E-cad(<50))	0·02	n.s.	0·38	<0·01

*Excludes patients with distant metastasis at the time of surgery TNM, tumour node metastasis, E-cad(≥50), 50 per cent or more tumour cells staining positive for E-cadherin; E-cad(<50), less than 50 per cent of tumour cells expressing E-cadherin; n s., not significant. †Spearman rank correlation coefficient

patients in the E-cad(≥50) group had cervical lymph node recurrence, at 12 and 24 months; they received surgical treatment or radiation therapy and were alive at 53 and 45 months after initial treatment. One patient in the E-cad(<50) group had lung metastasis 3 months after surgery, which was treated surgically, and another suffered brain metastasis at 16 months, which was resected surgically. These two patients were alive at the time of writing (at 58 and 45 months). Including these four patients, and four who died from pneumonia with local and/or lymph node recurrence or haematogenous metastasis, distant metastasis occurred in three patients with E-cad(≥50) tumour and in 12 with E-cad(<50) tumour. On the other hand, local and/or lymph node recurrence was diagnosed in one patient with normal E-cadherin expression, in 12 with E-cad(≥50) and in ten with E-cad(<50). Thus, distant metastasis occurred more in patients with E-cad(<50) tumours than in those with E-cad(≥50) lesions ($P<0{\cdot}05$). Spearman rank correlation analysis for haematogenous recurrence in the postoperative period showed that E-cad expression ($r_S=0{\cdot}38$, $P<0{\cdot}01$) and blood vessel invasion ($r_S=0{\cdot}28$, $P<0{\cdot}05$) were significant variables. On the other hand, local and/or lymph node recurrence correlated only with T category ($r_S=0{\cdot}38$, $P<0{\cdot}01$) (*Table 5*).

Discussion

E-cadherin, a cell adhesion molecule, mainly regulates intercellular adhesion in epithelial tissues. Reduced E-cadherin expression is associated with tumour dedifferentiation, increased invasiveness and a high incidence of lymph node metastasis in a number of human carcinomas[12,13,15], including oesophageal carcinoma[16]. The purpose of this study was to evaluate whether E-cadherin expression correlated with the clinical outcome in patients with squamous cell carcinoma of the oesophagus. Of 62 patients with oesophageal cancer only eight (13 per cent) had tumours with normal E-cadherin expression; the rest (87 per cent) had tumours expressing reduced levels of E-cadherin. Although Bringuier *et al.*[17] described in their study of bladder carcinoma that tumours with only a minor fraction of non-E-cadherin-expressing cells should be able to invade and thus must be regarded as abnormal, the present patients with reduced E-cadherin-expressing tumour were divided into two groups to compare their clinical outcome.

In this study, overall survival was inversely correlated with E-cadherin expression and patients with normal E-cadherin-expressing tumours had a better prognosis than those with E-cad(<50) tumours when compared with all patients, with those having stage I or II disease, and with those who were not chosen for postoperative radiotherapy ($P<0{\cdot}05$). This is in agreement with previous studies on carcinoma of the head and neck[18], stomach[19], bladder[17] and prostate[20]. In all these studies, decreased or aberrant E-cadherin expression was associated with poor prognosis. Little is known, however, about the role of E-cadherin expression of the primary tumour in the development of metastasis and the site of recurrence. In the present study, a significant relationship was found between decreased E-cadherin expression *in vivo* and haematogenous recurrence following radical surgery. Patients with E-cad(<50) tumours had a higher incidence of haematogenous metastasis resulting in death than those with normal E-cadherin expression or E-cad(≥50) tumours. These results indicate that inhibition of E-cadherin function enhances the possibility of release of cancer cells from the primary site and that tumours with decreased E-cadherin expression might have a higher metastatic potential than those with preserved expression before radical surgery.

In this study, patients with E-cad(<50) tumours tended to suffer more from bone than from liver metastasis, although the expression of E-cadherin in the metastatic sites was not studied. Previous studies have demonstrated that patients with breast cancer with heterogeneous or no E-cadherin expression tended to have bone or lung metastasis rather than distant lymph node or liver metastasis[21], and that patients with gastric cancer with both preserved E-cadherin expression and reduced α-catenin expression had liver metastasis more frequently than those with the other phenotypic expression of both molecules[22]. Moreover, Mayer *et al.*[19] demonstrated that E-cadherin expression in most metastatic gastric carcinomas was stronger than in the primary tumour, in contrast to observations on infiltrated lymph nodes in head and neck squamous cell carcinoma[18,23]. These results suggest that the microenvironment of each organ might have a modulating or selecting role for E-cadherin in metastasis formation. This is similar to observations on cell lines transplanted into nude mice[24], and a relationship might exist between the pattern of E-cadherin expression and haematogenous metastatic sites. However, E-cadherin expression on the cell surface does not guarantee cadherin function, and other mechanisms may also lead to impaired E-cadherin function.

The function of cadherin is regulated by cytoplasmic proteins including catenins, through which cadherin is anchored to the cytoskeleton[25]. Recent studies have shown that loss of α-catenin expression is related to dysfunction of E-cadherin-mediated intercellular adhesion in the human lung cancer cell line PC9[26] and also that reduction in the E-cadherin level is associated with homozygous deletion of the α-catenin gene in the prostate cancer cell line PC3[27]. In a previous immunohistochemical study[28] on human oesophageal cancer, reduction of both α-catenin and E-cadherin expression was significantly associated with tumour dedifferentiation, infiltrative growth and lymph node metastasis, but reduction of α-catenin expression was more closely correlated with cancer invasion and metastasis than E-cadherin. Additionally, dysfunction of cadherin-mediated interactions can be produced by increased tyrosine phosphorylation of β-catenin[29] or E-cadherin gene mutations[30]. Thus, for E-cadherin to be fully functional in the maintenance of epithelial integrity, the appropriate post-translational modification as well as the expression of cadherin-associated proteins including cadherin itself must be in place.

While further studies are necessary to elucidate the implications of modified cell adhesion molecule expression in cancer tissues, the present results suggest that patients with tumours of the oesophagus that express abnormal levels of E-cadherin have a poorer prognosis and a higher potential for bloodborne recurrence after operation than those with tumours expressing normal levels. The evaluation of E-cadherin expression may have predictive value for haematogenous recurrence in patients with oesophageal squamous cell carcinoma, and may serve as a guide to planning adjuvant therapy after surgery.

Acknowledgements

The authors thank Yaeko Naitou and Kyoko Tamura for assistance in the preparation of this manuscript and Jyunichi Tanimura for statistical help.

This work was supported in part by a grant-in-aid for cancer research from the Ministry of Education, Science and Culture (05 671 062) and the Ministry of Health and Welfare (5–12), Japan.

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British Journal of Surgery 1996, **83**, 1614–1615

Short note

Gastric tonometry and drain amylase analysis in the detection of cervical oesophagogastric leakage

A. MACHENS, C. BUSCH, Hw. BAUSE* and J. R. IZBICKI

*Departments of General Surgery and *Anaesthesiology, University of Hamburg, Martinistrasse 52, D-20246 Hamburg, Germany*

Correspondence to: Mr J. R. Izbicki

Cervical anastomotic leakage following oesophagectomy and gastric pull-up is still fraught with substantial morbidity and mortality[1]. Early detection of leaks is a prime goal with a view to reducing morbidity and mortality related to anastomotic leakage. A novel approach to the early detection of subclinical leaks is offered by gastric tonometry (GT) and drain amylase analysis (DAA). In this study, GT and DAA were prospectively assessed for suitability to detect oesophagogastric leaks early.

Patients and methods

Twelve patients with oesophageal cancer of the middle and distal third, one with bronchial carcinoma infiltrating the oesophagus and one with oesophageal perforation following bouginage for achalasia underwent subtotal oesophagectomy with gastric pull-up and oesophagogastric reconstruction. A gastric tonometer (Tonometrics, Worcester, Massachusetts, USA) was positioned 2 cm distal to the cervical oesophagogastric anastomosis and a cervical drain (Medimex SiliDrain; Medimex, Hamburg, Germany) placed near the anastomotic site. In compliance with the manufacturer's instructions[2], intramucosal pH ($\mathrm{pH_i}$) measurements were made after anastomotic completion and daily thereafter at 09.00 hours. Cervical drain fluid was collected daily for amylase determination. Mezlocillin and metronidazole were administered around the time of operation. A Gastrografin (Schering, Berlin, Germany) swallow was performed on day 7 to check for cervical leakage. When cervical leakage was clinically suspected as a result of local inflammation at the anastomotic site or when air or saliva was found in the cervical drain bag, the neck wound was opened widely and explored thoroughly. Cervical leaks confirmed on exploration of the neck wound were termed 'major', in contrast to those 'minor' leaks identified only in routine contrast studies.

The DAA reference values obtained in the prospective study were assessed in a retrospective analysis of major oesophagogastric leaks (1992–1994) following subtotal oesophagectomy with gastric pull-up and cervical oesophagogastric reconstruction. There were 33 oesophageal cancers of the middle and distal third (mostly squamous cell carcinoma), one malignant melanoma of the oesophagus and two oesophageal perforations (one spontaneous and one secondary to bouginage) in this retrospective group. This group did not differ from the prospective group with regard to median age, sex, surgical approach, oesophageal pathology, tumour stage or frequency of major cervical leaks.

Results

In the prospective group, two minor asymptomatic and four major, non-fatal, cervical leaks were diagnosed. The minor leaks were diagnosed by routine Gastrografin swallow on day 7. The major leaks manifested by local inflammation at the anastomotic site (two patients on days 3 and 10) or by air (one patient on day 1) or saliva (one patient on day 10) in the cervical drain bag. Median drain amylase activities in patients with leakage (major and minor leaks combined) were 231, 3342, 1606, 5258 and 2460 units/l (*versus* 277, 120, 73, 40 and 42 units/l in the control group) in the first 5 days. The median $\mathrm{pH_i}$ in patients with leakage (combined leak group) was lower than in the controls immediately after surgery and on the following 5 days: 7·12 *versus* 7·15, 7·16 *versus* 7·21, 7·12 *versus* 7·34 ($P = 0{\cdot}04$, Mann–Whitney U test), 7·19 *versus* 7·31, 7·23 *versus* 7·33 and 7·18 *versus* 7·27. The $\mathrm{pH_i}$ values for the two late (after day 3) leaks were generally lower than those for the two early leaks (within the first 3 days).

Table 1 Prediction of major and minor oesophagogastric leaks by gastric tonometry (intramucosal pH on day 2) and drain amylase analysis

	No leak	Leak	Total	P*
$\mathrm{pH_i}$ on day 2 (GT)†				
≥ 7·20	4	1	5	
< 7·20	2	5	7	
Total	6	6	12	0·24
Drain amylase activity (units/l)‡				
≤ 600	8	1	9	
> 600	0	5	5	
Total	8	6	14	0·003

GT, gastric tonometry. *Fisher's exact test (two tailed). †Sensitivity 80 per cent, specificity 67 per cent, positive predictive value 71 per cent, negative predictive value 80 per cent and accuracy 75 per cent. ‡Sensitivity 80 per cent, specificity 67 per cent, positive predictive value 100 per cent, negative predictive value 89 per cent and accuracy 93 per cent

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Paper accepted 12 January 1996

Cut-off levels at 7·2 for pH_i on day 2 and 600 units/l for cervical drain amylase appeared to be most suitable for early leak detection (*Table 1*). Unlike GT, DAA was able to detect major and minor cervical leaks at an asymptomatic stage. If only major leaks were considered, the predictive properties of GT for early leak detection decreased further, whereas DAA continued reliably to detect major leaks early (sensitivity 100 per cent, specificity 90 per cent, positive and negative predictive values 80 and 100 per cent respectively, and accuracy 93 per cent). It is noteworthy that two tonometers were lost by day 2 in delirious patients.

The additional time possibly gained from DAA was calculated by a retrospective review of previous leaks following subtotal oesophagectomy and gastric pull-up (*Table 2*). These were detected clinically at a mean of 5·5 days, which was 2·1 days more than for leaks detected by DAA.

Table 2 Retrospective review (1992–1994) of major non-fatal oesophagogastric leaks

Patient No.	Day of clinical evidence (mean 5·5 days)	Day of chemical evidence (drain amylase analysis)	Time gain (days) (mean of 2·1 days)
1	1	3	0
2	2	Negative	0
3	2	1	1
4	3	2	1
5	4	1	3
6	5	4	1
7	5	Negative	0
8	7	Negative	0
9	10	2	8
10	10	1	9
11	11	Negative	0

Discussion

By virtue of its ability to detect the decrease in pH_i that precedes systemic complications, GT has gained recognition in monitoring critically ill patients[3,4]. However, its usefulness in identifying anastomotic ischaemia, possibly indicative of imminent anastomotic breakdown, has not yet been defined.

A weak overall trend towards lower pH_i values at the anastomotic site was observed in patients with oesophagogastric leakage following oesophagectomy and gastric pull-up. However, this association was too weak to be clinically useful. Similar results were obtained by Jacobi *et al.*[5] after serial measurements of gastric submucosal tissue oxygen tension at the oesophagogastric anastomosis with a Clark-type oxygen electrode. The pH_i value in patients with late leak formation (after day 3) was lower than in those with early leak formation (within the first 3 days). These findings suggest that factors other than local oxygenation of the anastomotic site are more important in early leak formation where the pH_i was higher.

Following anastomotic breakdown oozing saliva may be conveyed to the surface by the cervical drain. The present data indicate that more than half of these leaks are chemically detectable by DAA a mean of 2·1 days ahead of clinical evidence. Some leaks may escape early chemical detection, with saliva passing the cervical drain, only to manifest later.

Although there was a trend towards lower pH_i values in patients with leakage, GT was of little clinical benefit in identifying cervical leaks ahead of clinical or radiological evidence. In contrast, DAA appears to be useful in detecting major oesophagogastric leaks at an early asymptomatic stage in a subset of patients. On the basis of these preliminary data, routine use of DAA for chemical evidence of early leaks is advocated to complement clinical and radiological surveillance.

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British Journal of Surgery 1996, **83**, 1616–1619

Experimental oesophagogastric anastomosis: preliminary report of a new compression device that also fragments

C. REBUFFAT, R. ROSATI*, U. FUMAGALLI*, F. VAROLI, G. ROVIARO and A. PERACCHIA†

*Department of General Surgery, Ospedale San Giuseppe and †Department of General and Oncological Surgery, Ospedale Maggiore Policlinico, University of Milan, *Department of General Surgery, Istituto Clinico Humanitas, Rozzano (MI), Italy*
Correspondence to: Dr R. Rosati, Istituto Clinico Humanitas, Via Manzoni 56, 20089 Rozzano (MI), Italy

Fifteen Beagle dogs underwent oesophagogastric anastomosis with a new device which enables a 'sutureless' compression anastomosis. The device fragmented and was passed in bits anally without causing obstruction. Immediate bursting pressure, tested in five dogs, was between 175 and 190 mmHg. The anastomoses of the remaining dogs were examined macroscopically and microscopically from day 6 to day 30. Healing was excellent with good muscular apposition and minimal residual inflammation.

Sutured and stapled intestinal anastomoses have excellent results[1] but the material persists in the tissues for much longer than is necessary[2]. Suture persistence may not only interfere with imaging (in the case of staples) but also may interact biologically to enhance anastomotic recurrence of both colorectal cancer[3–8] and Crohn's disease[9]. In the former an experimental 'sutureless' anastomosis induces fewest cancers[3,6,8]. Crohn's disease is related to macrophage activity, and granulomas are often an important histological feature. *In vitro* both absorbable and non-absorbable suture materials interfere with macrophage function and thereby might supply a mechanism for recurrence at the anastomosis[9].

Sutureless intestinal anastomosis can be achieved with compression devices[10–13], laser welding[14–16] and glues[17], but at present only compression devices are safe for use in humans[11,13]. Compression devices were first introduced by Denans in 1827[18]. Until recently, the most successful were the Murphy button[19] and the Boerema button[20]. In recent times the Russian AKA guns (2 and 4)[11] and the Valtrac (Davis and Geck, American Cyanamid, Danbury, Connecticut, USA) biofragmentable anastomotic ring (BAR) have been used with success[21–23].

Unless the button is particularly small, or fragments, there is a risk that it will impact in the terminal ileum and cause intestinal obstruction. This has limited the use of the AKA guns to colorectal surgery[11]. The BAR is not so limited, but then it is not strictly a sutureless technique. A purse-string suture is placed on both bowel ends and tied on to the central spindle of the device, which is then closed. The BAR is made of polyglycolic acid, and gradually dissolves over 2 weeks. During this time the ends of bowel are held together inverted on the spindle. As the device does not exert compression, when it fragments it leaves the inverted rim with its contained purse-string sutures, which is why it is not strictly a sutureless technique. Clearly, the purse-string material should be absorbable, but even absorbable material may interfere with macrophage function.

A new device is described that supplies a sutureless compression anastomosis with the added advantage that it fragments and is therefore suitable for use above the ileocaecal valve.

Materials and methods

Fragmentable anastomotic button

This consists of three polypropylene rings: inner, intermediate and outer. The outer ring is itself composed of two interlocking parts, male and female. Each individual ring (of which there are four: one inner, one intermediate and two outer, male and female) can break up into four component parts, which makes a total of 16 smooth fragments (*Fig. 1*). The inner and intermediate rings are held together by the applicator; the outer rings have a continuous portion, which is removed by the applicator's circular blade. The prototypes used in the present study were 25 mm in external diameter, and the single fragments were small, thin plastic plates of maximum dimension 18 × 12 × 1 mm.

The key to the device is the outer female ring. When the button contains tissue, tissue pressure forces the components of this ring apart, the wings interlock and the integrity of the ring is maintained (*Fig. 2*). As time passes, compression causes the trapped tissue to necrose while anastomotic healing takes place outside the area of compression. The whole button will thus detach from the anastomotic site and fall into the intestinal lumen. This, as shown by previous experimental and clinical studies with a similar, but non-fragmentable, compression anastomotic button in colonic surgery[12,13], occurs uneventfully a mean of 3 days after operation in the animal and after 11 days in the human being. Necrosis of the tissue trapped into the button

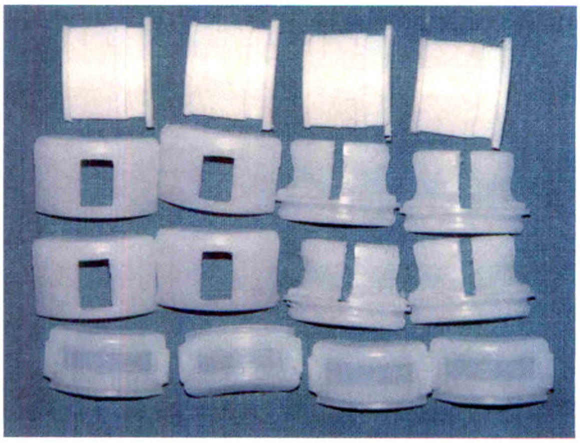

Fig. 1 The 16 fragments (four fragments each for the inner, intermediate, outer male and outer female rings respectively) of the anastomotic button

Paper accepted 14 January 1996

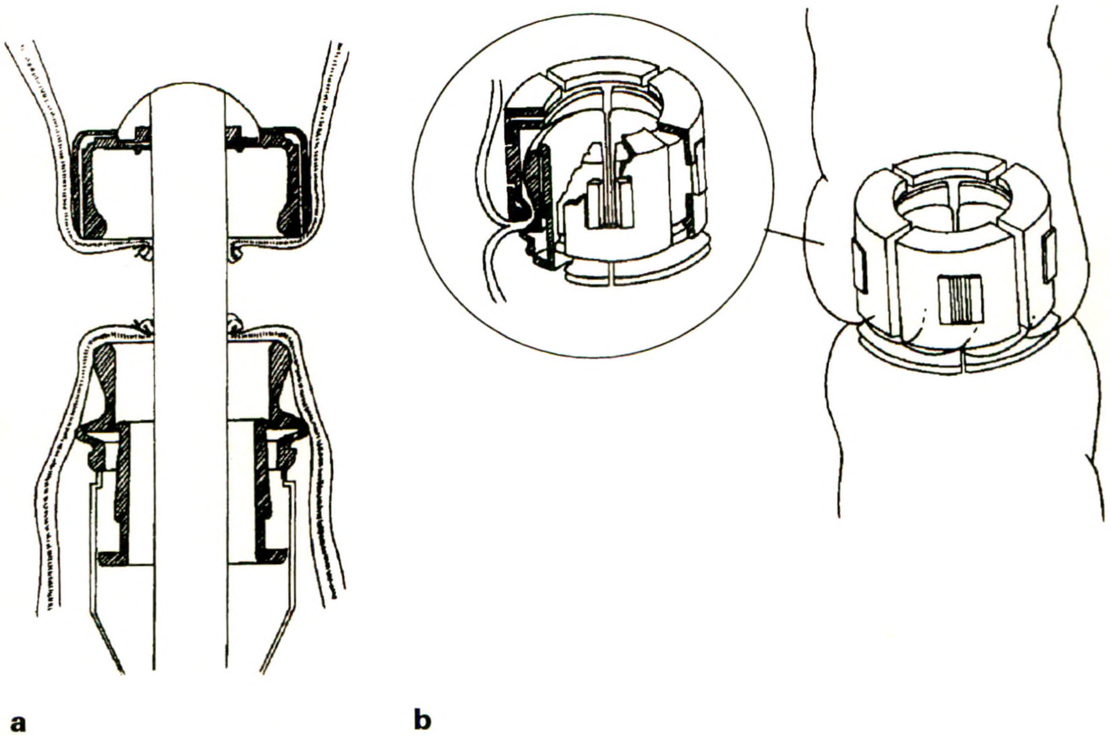

Fig. 2 Diagram of the mechanism of use of the gun and compression button. **a** After placement of two purse-string sutures on the bowel ends, the gun is inserted into the lumen, the purse-string sutures are tied and the device is approximated. **b** After firing, the button lock compresses the bowel ends, the circular blade cuts the tissue doughnuts tied by the purse-string sutures and detaches the button from the gun, which can be withdrawn with no additional manoeuvre. The button stays in place until anastomotic healing causes the whole button to detach. Fragmentation occurs a few hours after detachment of the button from the anastomotic site

causes a corresponding fall in tissue pressure inside the assembled button and thus the outer female ring becomes flabby, the wings unlock and the whole device disintegrates shortly after the button's detachment from the anastomosis (a few hours in the dog).

Fig. 3 shows the device mounted on a gun just after it has been fired on to foam (the white fluffy rim). In the button with an outer diameter of 25 mm, the inner lumen is 12·5 mm. A larger button with an outer diameter of 30 mm has an inner lumen of 17·5 mm to facilitate transit of gas and faeces through the button.

Surgical technique

Fifteen Beagle dogs (weight range 8·5–13 kg; ten females) underwent laparotomy under general anaesthesia. The distal oesophagus was transected and a purse-string suture was placed on the proximal end. The distal oesophageal end was used to introduce the gun. The central shaft of the gun was thrust through the anterior wall of the gastric fundus and the anvil (outer ring) was assembled. An end-to-side oesophagogastric anastomosis was created with the button, the gun was withdrawn and the distal oesophageal end was closed with sutures. Tissue doughnuts are released with this technique and they were inspected. Pyloroplasty was performed to facilitate gastric emptying. The dogs drank freely from the first postoperative day and started eating homogenized meat from either the second or third day, returning to a normal diet on day 7.

Bursting pressure

Five dogs were killed immediately after operation. The thoracic oesophagus was divided 6 cm proximal to the anastomosis and the stomach was divided at its upper third. The oesophageal stump was connected through a pressure transducer to a chart recorder and the stomach was held close with a crushing clamp. The specimen was then placed under water and inflated with air until one of the anastomotic ends slipped out of the button.

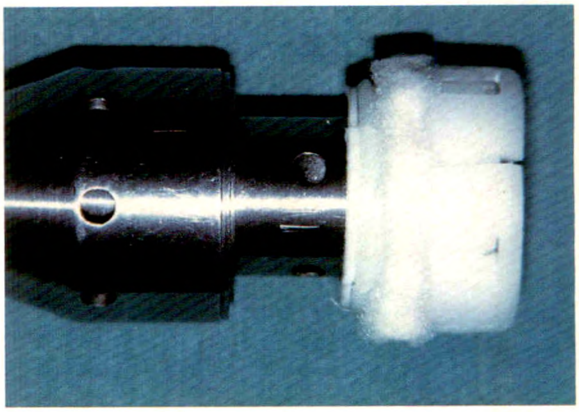

Fig. 3 Device mounted on a gun and fired to show closure of the device. The white foam is visible within the closed device

Results

There were no technical problems with the gun, despite the thickness of the oesophagus and stomach of the dog. All doughnuts were complete and the gun released with ease.

Bursting pressure

One of the anastomotic ends slipped out of the button, leading to disintegration of the assembly, at a median of 178 (range 175–190) mmHg.

Clinical evaluation

Two dogs died from an unrelated cause on days 6 and 7. They both had an intrathoracic volvulus of herniated stomach which caused cardiac embarrassment. There were no signs of infection and the anastomoses were intact and healthy.

The remaining eight dogs were well and ate normally, but with occasional reflux and vomiting in some. Of the ten dogs not killed immediately, button fragments were found in the stools of seven between days 5 and 8 after operation. In the remaining three dogs, fragments were found within the small bowel at necropsy, with no evidence of obstruction.

Histological evaluation

The anastomoses of the two dogs that died on days 6 and 7, and of three other dogs killed on day 10, were macroscopically intact. Haematoxylin and eosin-stained sections showed good alignment of all layers of the bowel wall and mucosal regeneration.

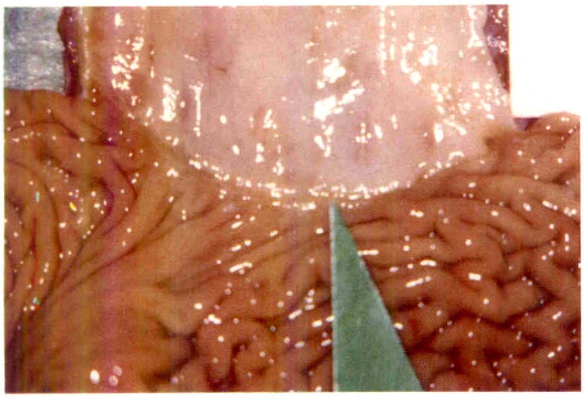

Fig. 4 Macroscopic appearance of an oesophagogastric anastomosis after 30 days, seen from the mucosal side. The anastomotic line is flat and no overgrowing scar tissue is detectable

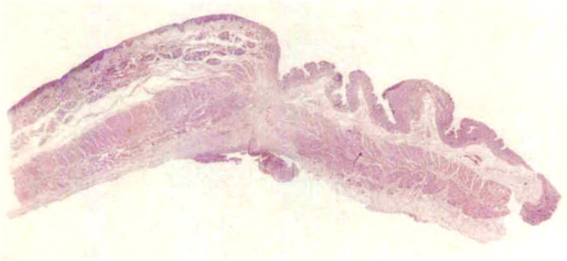

Fig. 5 Microscopic evaluation of the same anastomosis after haematoxylin and eosin staining. There is good alignment of wall layers, satisfactory mucosal re-epithelization of the anastomotic line and no chronic inflammatory reaction. (Original magnification ×25)

The remaining five dogs were killed after 30 days. Their anastomoses could be identified with the naked eye, largely because of the macroscopic differences between oesophagus and stomach but were otherwise hard to see (*Fig. 4*). Longitudinal section confirmed good alignment of the layers of the bowel wall with some parakeratosis in the oesophageal squamous epithelium (*Fig. 5*).

Discussion

The authors have been encouraged by the success of this new anastomotic button. The instrument handled well during operation and has the advantage that the introducer is similar in most respects to an anastomotic stapling gun. This means that difficult colorectal and oesophagogastric anastomoses could be attempted in the same way as now performed conventionally. This is an advantage over the BAR, which does not have a satisfactory introducer for performing anastomosis in awkward positions[22].

The button fragmented well in all cases and passed in small and smooth bits without causing obstruction, notwithstanding the small size of the dogs used in this study (maximum weight 13 kg). Oesophagogastric anastomosis was chosen deliberately to test this ability maximally, although it must be accepted that surgical pyloroplasty obviated problems at the first narrow point. Impaction of the button fragments did not occur in this study and, owing to the small size of the fragments (which are smooth and thin), seems unlikely to happen. However, further experimentation is necessary for this purpose.

Some surgeons might be concerned about the early time at which fragmentation occurs (around 5 days in the dog). However, it must be pointed out that fragmentation occurs only after the button has detached unfragmented from the healed anastomosis, when no more tissue is trapped within the button itself. In fact, clinical experience of colorectal anastomoses with AKA guns[11] and with an earlier prototype of this button which did not fragment[12,13] has been good; the buttons are usually passed around 10 days after operation. Furthermore, both with stapled and sutured anastomoses, the materials themselves encircle small islands of tissue which swell after operation, thereby increasing tissue tension. Over a similar time scale, this probably causes conventional anastomoses to suffer a similar microscopic loss of support from their anchoring sutures or staples[2], as occurs with the AKA compression anastomosis. The difference is that, to the naked eye, the sutures remain at the anastomotic site and seem still to be exerting an influence.

In an experimental setting of cortisone-induced delayed anastomotic healing, compression was shown to be as good as that associated with stapling[24]. This is probably due to the fact that compression induces only minimal local inflammation, which is considered one of the most important causes of anastomotic weakness because it increases the so-called 'lag period' of healing.

With this button, as with other compression devices, there is good macroscopic and histological healing. In both end-to-end and end-to-side anastomoses mucosal epithelization occurs earlier than with sutures or staples owing to the absence of foreign material. Thus the anastomosis, which appears as a thin line and it is often mistaken for a mucosal fold, has no overgrowing inflammatory tissue reducing its lumen. As a result, reported clinical series of compression anastomosis in colonic surgery have minimal, if any, incidence of stenosis.

An ideal anastomotic material would last in the tissue for as long as necessary and then disappear. This would make anastomotic support optimal and side-effects of retained materials (now known to exist experimentally) would be obviated[2,10]. Sutureless techniques may well supply this ideal, with this new button showing promise as it extends the applicability of compression anastomosis throughout the gastrointestinal tract.

Acknowledgements

Special thanks are due to Professor R. K. S. Phillips for support and appreciation of this work.

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British Journal of Surgery 1996, 83, 1620–1622

Salvage treatment for inoperable neck nodes in head and neck cancer using combined iridium-192 brachytherapy and surgical reconstruction

P. G. S. CORNES, H. J. COX, P. R. RHYS-EVANS, N. M. BREACH and J. M HENK

The Head and Neck Unit, Royal Marsden Hospital, London, UK
Correspondence to: Dr P G. S. Cornes, Academic Unit of Radiotherapy, Royal Marsden Hospital, Downs Road, Sutton SM2 5PT, UK

The results of debulking surgery and re-irradiation with radioactive implants (brachytherapy) are reported for 39 patients with inoperable metastatic neck nodes from primary head and neck cancers. For 13 patients conventional salvage by partial debulking surgery and brachytherapy proved effective, with 68 per cent control at 1 year, but six patients suffered severe radiation fibrosis, necrosis and contractures. Some 26 patients were treated by combined tumour debulking, skin resurfacing and brachytherapy implant. Initial tumour control and freedom from serious toxicity was achieved in 24 patients. Local control was achieved in 63 per cent of patients at 1 year, with a serious morbidity rate of 12 per cent.

Head and neck cancers commonly metastasize to cervical lymph nodes, but even in these advanced cases cure is often achieved by neck dissection, radical radiotherapy or a combination of the two. Subsequent relapse in the neck after combined therapy is infrequent[1]. However, in patients with the poor prognostic signs of positive resection margins or extracapsular spread the risk of relapse may be as high as 41 per cent at 5 years[2].

Most patients with neck node recurrence also relapse at the primary or distant secondary sites, and survival is limited[3]. However, 7 per cent of patients in whom the neck is the solitary site of recurrent head and neck cancer survive for 6 months or more[3], and treatment is warranted to control the distressing symptoms.

If the disease is fixed and inoperable, and the neck has already been irradiated to a radical dose, the options for salvage treatment by surgery or radiotherapy[4] are limited. Chemotherapy offers few complete responses, which take time to be achieved[5–7].

Interstitial irradiation (brachytherapy) is the surgical implantation of radioactive sources within and around the tumour. This permits a high dose to be delivered to the tumour, with a rapid fall off of radiation dose to the surrounding uninvolved tissues. Brachytherapy has been used to re-treat malignant neck nodes but, as with external-beam re-irradiation, tissue fibrosis and necrosis occur with increasing volume of the neck treated[8], resulting in contracture and ulceration similar to that in uncontrolled cancer.

This paper describes the authors' experience of brachytherapy re-irradiation of isolated neck relapses of head and neck cancer, and the evolution of combined surgery and brachytherapy following an initial report[9] in five patients. It also describes the longer-term experience with this modified technique, and compares the outcome in these patients with that in those treated by the original salvage technique of debulking and brachytherapy re-irradiation only.

Patients and methods

Thirty-nine patients had been treated for primary head and neck tumour with curative intent. All had received radical-dose radiotherapy to the neck and many had also undergone neck dissection. All had neck disease that was fixed to deeper structures, such that clear surgical margins could not be obtained by reoperation. Preoperative investigations confirmed disease control at the primary tumour site, with no evidence of distant metastasis.

Squamous cell carcinoma and mucoepidermoid carcinoma were the histological diagnosis in 30 patients The remaining patients had adenocarcinoma, adult soft tissue sarcoma and thyroid carcinoma. The commonest primary sites were the oral cavity (nine patients), oropharynx (six), salivary gland (five) and larynx (six) The mean age of the patients was 63 (range 21–75) years. All had received radical-dose radiotherapy to the neck with a mean dose of 53·4 (range 40–76) Gy. Mean (range) dose was equivalent in both the original and modified treatment groups (57 (40–76) Gy in the original patients (group 1), 52 (40–76) Gy in those having modified therapy (group 2)). Twenty-five per cent of patients had undergone previous radical neck dissection.

In patients in group 1 the neck disease was approached through the previously irradiated skin This was elevated and the underlying tumour debulked. Nylon cannulas, 5 mm in diameter, were placed across the tumour bed parallel to each other, 1·2–1·5 cm apart The cannulas were led to the skin at each end, and the skin was closed. The cannulas were loaded with radioactive iridium-192 wire as soon as early wound healing had occurred (postoperative days 4–10). The radiotherapy dose was calculated by means of the Paris rules[10], with the dose designed to deliver approximately 10 Gy of radiation per day to the reference isodose. The mean brachytherapy dose was 49·5 Gy (at reference isodose) over 5 days.

The active wires were removed at the end of treatment, and the cannulas withdrawn on the ward. The patients were then allowed home.

For patients in group 2 the technique was modified. Previously irradiated skin was excised over the planned treatment area. As much of the tumour as possible was excised, and hollow cannulas were placed in parallel rows as before. The site was resurfaced using pedicled cutaneous or myocutaneous flaps from an unirradiated donor site. Some 17 deltopectoral, seven pectoral major and two latissimus dorsi flaps were used; no free flaps were employed. The cannulas were loaded with radioactive iridium-192 wires as before. The mean dose was 49·8 Gy over 5 days.

Local control was assessed at follow-up and the probability of freedom from local relapse at the treated site was calculated by the Kaplan–Meier method[11]. Late side-effects from radiotherapy were graded for permanent injury by means of the joint scoring system of the European Organization for Research and Treatment of Cancer (EORTC) and the Radiotherapy and Oncology Group of the USA (RTOG). This records toxicity with

Paper accepted 19 January 1996

Table 1 Scale of late toxicity scoring for skin and subcutaneous tissues*

Grade	Description
Severe	
5	Death from toxicity
4	Necrosis or ulceration
3	Fibrosis with more than 10 per cent contracture Gross telangiectasia
Moderate	
2	Fibrosis with less than 10 per cent contracture Patchy atrophy Moderate telangiectasia
Mild	
1	Slight atrophy Loss of subcutaneous fat

*System of the European Organization for Research and Treatment of Cancer and the Radiotherapy and Oncology Group of the USA

Table 2 Grades of severe late radiation toxicity* in the two treatment groups

Grade	Group 1 ($n=13$)	Group 2 ($n=26$)	Total ($n=39$)
5	0	0	0
4	4	0	4
3	2	3	5
Total	6	3	9

*System of the European Organization for Research and Treatment of Cancer and the Radiotherapy and Oncology Group of the USA

a five-point scale, with serious symptomatic toxicity graded 3, 4 and 5 (*Table 1*).

Early surgical complications are described individually.

Results

Local control was initially obtained in all patients in groups 1 and 2, who now have a mean follow-up of 14 (range 3–53) months.

Overall survival of the patients was limited, with a 38 per cent probability of survival to 24 months. Some 24 of the 39 patients have now died. All who died, died from the cancer. One patient died from solitary relapse in the salvage site in the neck, three died from relapse at the primary site and 20 from metastatic disease. Four patients have remained disease free for more than 3 years.

The overall actuarial probability of local control in the neck was 63 per cent at 1 year from the time of the procedure.

In group 1 minor surgical complications occurred in four of 13 patients, consisting of two cases of delayed wound healing, one postoperative haematoma and one salivary fistula. All resolved without intervention. In group 2 seven minor surgical complications occurred in 26 patients, consisting of six cases of delayed wound healing and one chyle fistula. All resolved without intervention.

There were two major surgical complications, both in group 2. One was a wound dehiscence that required a split skin graft, the other being acute haemorrhage from the undersurface of a deltopectoral flap on the fourth postoperative day. The latter patient required a 4-unit blood transfusion and a second latissimus dorsi flap to repair the defect. Neither of these complications could be attributed to irradiation.

Table 3 Early surgical complications in the two treatment groups

Grade	Group 1 ($n=13$)	Group 2 ($n=26$)	Total ($n=39$)
Fatal	0	0	0
Severe	0	2	2
Moderate	4	7	11
Total	4	9	13

Radiation toxicity for the two groups is compared in *Table 2*, using the EORTC–RTOG grading described in *Table 1*. Acute surgical morbidity is compared in *Table 3*.

Discussion

The modified technique of debulking surgery, skin resurfacing and brachytherapy re-irradiation has enabled total doses of up to 127 Gy to be delivered to the neck (mean total dose 103 (range 85–127) Gy). As animal data have suggested, the deep structures of the neck have withstood irradiation to twice the conventional tolerance dose for external-beam radiotherapy[12,13].

Before the modification of the operative technique, patients in group 1 suffered an unacceptable (six of 13 patients) rate of serious morbidity (EORTC–RTOG grade 3 or more). The symptoms were due to chronic non-healing ulceration or severe contractile cutaneous and subcutaneous fibrosis. They were as severe as those of the progressive cancer that the treatment was described to avoid.

The addition of resurfacing with unirradiated skin reduced serious toxicity to only three of the 26 patients in group 2. The three cases were all of the lowest grade (3) of serious morbidity, as no death, necrosis or ulceration occurred in this group. Overall, patients in group 2 achieved initial tumour control and freedom from serious treatment-related morbidity in 24 of 26 cases.

The deltopectoral and attached myocutaneous flaps have proved to be a reliable and rapid means of transferring unirradiated skin to the retreatment site. Previous studies[14,15] had suggested that there is a high risk of failure when transferring these flaps into sites of previous radiotherapy treatment.

Compared with the other limited treatment options in this group of patients, symptom control was achieved rapidly. Hospital stay was as short as 14 days. Both factors are important in a patient group where overall survival is limited. The complication rate was acceptable provided the neck skin was replaced with a pedicled flap. For all these reasons, the modified treatment of tumour debulking, skin resurfacing and brachytherapy should be regarded as standard salvage treatment for patients with head and neck cancer who relapse with isolated inoperable neck disease after previous radiotherapy.

Acknowledgements

This work was supported financially by the Head and Neck Unit Research Fund, Royal Marsden Hospital, London, UK.

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British Journal of Surgery 1996, 83, 1623–1652

Surgical Research Society Abstracts

The following abstracts were presented at the 84th meeting of the Surgical Research Society, with Professor Sir David Carter in the Chair. The meeting was organized by the Department of Surgery, University of Birmingham, and held on 27–28 June 1996 in the University of Birmingham. Ninety-seven papers were presented during the scientific sessions, into which was integrated a lecture entitled 'Gene therapy for surgical cancers' delivered by Dr M. T. Lotze, MD. The Patey Prize was awarded to Mr T. R. L. Griffiths for his paper entitled 'Proto-oncogene expression and bladder cancer: *c-myc* is associated with apoptosis'.

Stimulus–secretion coupling in acute pancreatitis: specific defect in acinar cell secretory pole calcium signalling

J. B. Ward, H. Morris, M. Hashmi, R. Sutton and O. H. Petersen, *Department of Surgery and The Physiological Laboratory, University of Liverpool, Liverpool, UK*

Disruption of secretion may be an important event in acute pancreatitis Cytosolic calcium ($[\mathrm{Ca}^{2+}]_i$) is a key messenger within the acinar cell: secretory pole $[\mathrm{Ca}^{2+}]_i$ oscillations following secretagogue stimulation initiate normal exocytosis. The normal oscillatory $[\mathrm{Ca}^{2+}]_i$ signal is lost during experimental pancreatitis. This study examined spatial aspects of the $[\mathrm{Ca}^{2+}]_i$ signal and the intracellular calcium pools during caerulein-induced pancreatitis

Mice received hourly injections of caerulein 50 μg kg⁻¹ or saline (controls). Pancreata were harvested after injections 1, 3, 5 and 7, acini isolated with collagenase and cells loaded with fura-2 The pattern of $[\mathrm{Ca}^{2+}]_i$ release in response to acetylcholine (ACh) was assessed using digital imaging The intracellular pools and pattern of calcium extrusion were assessed with the endoplasmic reticulum calcium adenosine 5′-triphosphate (ATP)ase inhibitor thapsigargin.

On stimulation with ACh 500 nmol l^{-1} the proportion of experimental cells maintaining a normal polarized increase in $[\mathrm{Ca}^{2+}]_i$ progressively diminished: 16 of 17 after one, 12 of 18 after three, six of 13 after five, and three of six after seven injections ($\chi^2_{\mathrm{trend}} = 7{\cdot}38$, $P < 0{\cdot}01$). A high proportion of control cells maintained a normal signal. Following thapsigargin there was no significant difference between experimental and control cells in the amplitude of $[\mathrm{Ca}^{2+}]_i$ increase: between mean (s.e.m.) 154(12·9) and 346(34·1) nmol l^{-1} in experimental cells, and between 243(10·5) and 382(17·6) nmol l^{-1} in controls, suggesting that these stores were not depleted. There was no significant difference in the rate of calcium extrusion.

These data suggest that during early caerulein hyperstimulation calcium reuptake into the endoplasmic reticulum is preserved, but there is a specific disruption of physiological $[\mathrm{Ca}^{2+}]_i$ signalling in the secretory pole of the acinar cell. These changes may contribute to the disruption of secretion that occurs in the pathogenesis of acute pancreatitis.

Role of vascular endothelial growth factor as a potential serum marker for colorectal cancer and metastatic disease

N. R. Cruickshank, D. F. Baban*, J. Budden*, J. D. Evans, D. Kerr*, J. P. Neoptolemos and L. W. Seymour*, *Department of Surgery, Queen Elizabeth Hospital and *CRC Institute for Cancer Studies, University of Birmingham, Birmingham, UK*

Increased expression of vascular endothelial growth factor (VEGF) has been identified in a variety of gastrointestinal cancers VEGF mediates a range of paracrine activities via receptors on vascular endothelial cells, most notably angiogenesis and vascular permeability. Increased levels of VEGF expression have been demonstrated using Northern blotting and reverse transcriptase–polymerase chain reaction in metastatic colorectal cell lines. These results indicate that VEGF may have a role in tumour dissemination.

In this study expression of VEGF was investigated in the serum of patients with colorectal cancer using an enzyme-linked immunosorbent assay. Carcinoembryonic antigen (CEA) levels were measured in the same samples. Preoperative serum samples were obtained from 48 patients with colorectal cancer and 30 normal volunteers.

Mean (s.d.) expression of VEGF in normal serum was 232(159) pg ml⁻¹ Some 40 per cent of tumours (stage A–D) expressed VEGF levels in excess of two standard deviations (530 pg ml⁻¹). Seven of eight patients with Dukes D (range 580–2000, mean(s.d.) 1038(513) pg ml⁻¹), four of nine with Dukes C (range 580–985, mean(s.d.) 766(206) pg ml⁻¹), five of 17 with Dukes B (range 680–1300, mean(s.d.) 943(231) pg ml⁻¹) and two of 12 with Dukes A (range 570–700, mean(s.d.) 635(91) pg ml⁻¹) disease had raised VEGF levels (χ^2 for trend of VEGF against Dukes stage 10·14, $2P < 0{\cdot}001$, Fisher's exact probability test).

Serum levels in the presence of liver metastases were significantly raised compared with those in all other groups ($2P < 0{\cdot}05$) and especially the normal population ($2P < 0{\cdot}0001$). CEA levels measured in the same serum samples showed no correlation with Dukes stage and VEGF.

These findings suggest that raised serum VEFG levels are associated with haematological metastases, increase with Dukes stage and indicate a possible role for serum VEGF as a marker of advanced disease

Immunosuppression and homologous blood transfusion

J. I. Spark, I. C. Chetter, R. C. Kester, P. J. Guillou and D. J. A. Scott, *Department of Vascular Surgery, St James's University Hospital, Leeds, UK*

Homologous blood transfusions may exert a generalized immunosuppressive effect. This study examined whether cell salvaged autologous blood (CSAB) could serve as an alternative to homologous blood (HBT) in elective abdominal aortic aneurysm (AAA) repair, and if this influenced the incidence of infective complications and duration of hospital stay. Prostaglandins have been shown to produce multiple effects on the immune system; the production of prostaglandin E_2 (PGE_2) and monocyte major histocompatibility (MHC) class II antigen expression was therefore measured

Forty patients, 34 men and six women of median age 71 (range 54–82) years undergoing AAA surgery were randomized to HBT ($n = 23$), or CSAB ($n = 17$). Peripheral blood was taken before operation, during the operation and for the first 7 days after surgery PGE_2 was determined using an enzyme immunosorbent assay and monocyte MHC class II expression by flow cytometry

Both groups received a median of 3 units of blood per patient The level of haemoglobin at discharge for the two groups was similar and there was no difference in perioperative mortality. Median duration of stay was 9 (range 7–13) days for the CSAB group and 12 (range 7–19) days for the HBT group ($P < 0{\cdot}05$, Mann–Whitney *U* test). There were three patients with infection in the CSAB group and eight in the HBT group (*P* not significant). PGE_2 concentration was maximum during the initial surgical insult with no significant difference between the two groups. Patients who received HBT had persistently raised levels of PGE_2 at 4 h after reperfusion, median 20·1 (interquartile range (i.q.r.) 13·9–26·7) *versus* 8·2 (5·6–9·9) pg ml⁻¹ for the

CSAB group ($P<0{\cdot}01$). Monocyte MHC class II expression was maximally reduced in those who received HBT on day 1 after operation, median 6·05 (i.q.r. 3·1–7·8) *versus* 12·7 (8·6–14·7) mean channel fluorescence for the CSAB group ($P<0{\cdot}01$). There was an inverse correlation between PGE_2 concentration and MHC class II expression ($r_s=0{\cdot}76$, $P<0{\cdot}05$, Spearman rank correlation).

CSAB can safely replace or at least decrease exposure to homologous blood transfusion and reduce hospital stay by 3 days. This study also provides evidence that HBT potentiates the immunosuppressive effects of surgery by increasing the PGE_2 level and resulting in impaired monocyte MHC class II expression.

Muscle configuration affects the force generated by the electrically-stimulated graciloplasty

B. J. Mander, R. Ratani, J. F. Abercrombie, B. D. George, P. J. Lunniss, J. Rogers and N. S. Williams, *Academic Department of Surgery, St Bartholomew's and London School of Medicine and Dentistry, London, UK*

During the development of the electrically-stimulated gracilis neoanal sphincter two principle muscle configurations were used. In this study the optimum configuration of the transposed muscle was determined with respect to the resting pressure and maximum force-generating potential of the muscle.

Between November 1989 and April 1995 30 patients underwent the procedure In 16 patients the muscle was transposed around the anal canal in an 'alpha' configuration (distal tendon sutured to the ipsilateral ischial tuberosity). In 14 patients a 'gamma' configuration was used, with the tendon sutured to the contralateral ischial tuberosity. The occluding pressure generated by the muscle was measured using water-filled microballoons both with the neosphincter turned off (basal neosphincter pressure, BNP) and at tetanic contraction (maximum neosphincter pressure, MNP)

	Alpha ($n=16$)	Gamma ($n=14$)
BNP (start of stimulation) (cm H_2O)	31 (23·5–41·6)	42·5 (30·1–49·8)
BNP (100 days of stimulation) (cm H_2O)	29·5 (22·2–38·6)	45 (32·5–51·7)
MNP (start of stimulation) (cm H_2O)	104 (91·5–137·8)	255 (210·7–378·5)
MNP (100 days of stimulation) (cm H_2O)	77·5 (62–95)	155 (126–223)

Values are median (95 per cent confidence interval)

There was no difference in the basal neosphincter pressure between the two groups at the start of stimulation although after 100 days it was higher in the gamma group ($P=0{\cdot}04$, Mann–Whitney *U* test). The gamma configuration generated a significantly higher maximum occlusion pressure at both the start of stimulation and after 100 days ($P=0{\cdot}0002$ and $P=0{\cdot}0007$ respectively). In both groups the maximum neosphincter pressure decreased during the period of muscle conversion (gamma $P=0{\cdot}0015$, alpha $P=0{\cdot}003$, Wilcoxon signed rank test)

It is concluded that the gamma configuration produces a greater dynamic occlusion pressure than the alpha configuration.

Interstitial deletions on the short arm of chromosome 8 in colorectal cancers

S. A. Chughtai, M. C. Crundwell, N. R. Cruickshank, M. Knowles, J. P. Neoptolemos and D. G. Morton, *Department of Surgery, University of Birmingham, Birmingham and Marie Curie Research Institute, Oxted, Surrey, UK*

In colorectal cancer two regions of interstitial loss have been reported on chromosome 8p, with a candidate tumour suppressor gene (TSG) being cloned to the telomeric locus (8p22).

Seventy-five matched colorectal tumours and serum samples have been analysed with 11 microsatellite markers spanning the centromeric region of chromosome 8p (p11·2–p12), to produce a detailed deletional map of this region.

Detailed analysis revealed two distinct regions of interstitial loss within this region. Isolated deletion of the region Ank-1-D8S255 (P1) was identified in nine of 71 cancers and of D8S87-D8S259 (P2) in 11 of 71 cancers. Loss of both loci was identified in seven tumours, and four tumours appeared to have lost the whole short arm.

Analysis of the results for clinicopathological parameters identified that P2 loss was associated with Dukes A cancers (five of 11 *versus* two of 59, $P=0{\cdot}0003$). A trend towards local invasion (14 of 16 *versus* 35 of 55, $P=0{\cdot}080$), poor differentiation and bloodborne metastases was noted in tumours with P1 loss.

This is the first study to report the presence of two separate interstitial deletions in the 8p12–p11·2 region in colorectal cancers. These results indicate the presence of two TSGs within the C8p12–p11·2 locus, and that inactivation of each of these genes has a different and independent role in colorectal progression. The study indicates that the putative TSG at the P1 locus conveys an invasive phenotype, whereas the TSG at the P2 locus is an earlier mutational event in colorectal Dukes A cancers.

Adenosine therapy for endotoxin-induced acute lung injury

M. C. Makunda, C. J. Kelly, N. Cregg, A. Leahy, R. Dwyer, R. G. K. Watson and D. J. Bouchier-Hayes, *Departments of Surgery and Anaesthesia, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin and Waterford Regional Hospital, Waterford, Ireland*

Acute lung injury resulting from endotoxaemia has been shown experimentally to be due to leucosequestration and release of humoral mediators including components of the complement system, cytokines and the arachidonic acid metabolites Adenosine *in vitro* and *in vivo* inhibits neutrophil activation and neutrophil-mediated endothelial cell injury. In addition, adenosine has contradictory vasodilator and vasoconstrictor effects, its influence on endotoxin-induced pulmonary hypertension being unclear. The aim of this study was to determine whether administration of adenosine has a protective effect on neutrophil-mediated lung injury and decreases endotoxin-induced pulmonary artery hypertension.

Sheep were randomized to endotoxin $1\,\mu g\,kg^{-1}$ ($n=6$); endotoxin + low-dose adenosine (LADO) $110\,\mu g\,kg^{-1}\,min^{-1}$ ($n=4$); or endotoxin + high-dose adenosine (HADO) $220\,\mu g\,kg^{-1}\,min^{-1}$ ($n=4$). Myeloperoxidase (MPO) activity measured pulmonary neutrophil influx. Pulmonary endothelial permeability was measured by wet to dry weight ratio (W:D). Mean arterial pressure, mean pulmonary artery pressure (MPAP), cardiac output, oxygen content and arterial hydrogen ion concentration were measured throughout.

	MPO		MPAP (mmHg)		
	(iu/ml)	W:D	0 min	30 min	60 min
Endotoxin	111·2(14)	3·7(0·8)	22·3(2·7)	40·3(5)*	33·2(2)†
LADO	125(10)	5·1(1·5)	21(2)	38·3(6·9)†	33(2·1)
HADO	116·7(28)	10·7(3)	19·8(1·5)	36(2·9)†	27·5(2·8)†

*$P<0{\cdot}005$, †$P<0{\cdot}05$ *versus* endotoxin

Administration of endotoxin resulted in a significant increase in pulmonary artery pressure, hypoxia and acidosis. Adenosine therapy did not alter these endotoxin-induced changes. In addition, adenosine therapy did not reduce pulmonary neutrophil infiltration or endothelial permeability, as measured by myeloperoxidase and wet:dry weights Contrary to *in vitro* human studies and other *in vivo* experimental studies, these data indicate that adenosine administration is of no therapeutic benefit in this model of endotoxaemia. This underlies the importance of evaluating novel therapies in large animal models before clinical evaluation.

Gene therapy for pancreatic cancer: bystander killing in pancreatic cancer cells using the nitroreductase/CB1954 approach

N. K. Green, D. J. Youngs, P. F. Searle*, L. S. Young*, D. J. Kerr*, C. J. Springer† and J. P. Neoptolemos, *Department of Surgery and *CRC Institute for Cancer Studies, University of Birmingham, Birmingham and †ICRF, Sutton, UK*

The treatment of advanced pancreatic cancer is limited by the low therapeutic index of many cytotoxic drugs. Virally directed enzyme prodrug therapy (VDEPT) uses expression of non-mammalian enzymes within tumour cells to catalyse local production of cytotoxics from non-toxic prodrugs. CB1954 has low toxicity to mammalian cells but is activated to a powerful bifunctional alkylating agent capable of forming interstrand DNA crosslinks, by the *Escherichia coli* enzyme nitroreductase (*ntr*) An important concept in the VDEPT approach is the 'bystander effect' which occurs when cytotoxic agents diffuse from transduced cells killing neighbouring untransduced cells. It is imperative that bystander killing occurs as with current gene transfer techniques it is impossible to introduce therapeutic constructs into 100 per cent of tumour cells.

SUIT2 pancreatic cancer cells were transduced with a retroviral vector (LNC-*ntr*) containing the *ntr* gene under the control of a cytomegalovirus (CMV) promoter. Clones were assayed for susceptibility to CB1954 using the sulforhodamine B (SRB) protein assay, screened for *ntr* protein expression by Western blotting, and the presence of the *ntr* gene in the clones was confirmed using polymerase chain reaction. Clones were isolated, which are up to 500-fold more sensitive to CB1954 than the parental cell line (IC_{50} values of 0·7–34 μmol l^{-1} CB1954 for transduced cells compared with 203–597 μmol l^{-1} for parental cell lines, $P<0{\cdot}001$, non-parametric analysis of variance). Clones were then assessed in 'mixing' experiments to determine whether 'bystander' killing occurs

Varying proportions of transduced and parental cells were mixed before addition of CB1954 and the percentage cell death determined by the SRB assay. When 50 per cent of the cancer cells expressed *ntr* there was 100 per cent cell death, with 30 per cent expressing 67–81 per cent cell death and even using only 10 per cent transduced cells levels of cell killing around 45 per cent were obtained ($P<0{\cdot}001$ compared with no bystander effect.)

These results demonstrate that when treated with CB1954 the clones in which *ntr* is expressed from the constitutive CMV promoter exhibit a significant 'bystander effect'. Clones containing *ntr* under the control of the tumour-specific promoter CEA are currently being screened which will allow tumour restricted expression of *ntr* following *in vivo* administration, and may lead to more effective therapies for the treatment of pancreatic cancer.

Proto-oncogene expression and bladder cancer: c-*myc* is associated with apoptosis

T. R. L. Griffiths*†, M. C. Robinson‡, R. Abdel-Fattah§, J. Lunec§, C. Marsh‡, B. K. Shenton* and D. E. Neal*†, *Department of *Surgery and §Cancer Research Unit, University of Newcastle, and Departments of ‡Pathology and †Urology, Freeman Hospital, Newcastle upon Tyne, UK*

In superficial (Ta and T1) bladder transitional cell carcinoma (TCC), 10–20 per cent of lesions show muscle-invasive progression. High p53 and epidermal growth factor receptor (EGFr) levels are associated with progression; p53 accumulation in superficial tumours is usually wild type and heterogeneous. In contrast, p53 accumulation in muscle-invasive tumours is often diffuse and mutant. *In vitro* studies suggest that c-*myc* is a putative induction signal for p53-dependent apoptoses. Aims were to assess (1) expression of c-*myc*, c-*fos* and c-*jun* measured by immunohistochemistry (IHC) and flow cytometry; and (2) associations with wild-type p53, apoptosis and EGFr.

Tumours from 147 patients with newly diagnosed TCC (60 Ta, 40 T1, 47 muscle-invasive) were collected. Frozen sections (c-*myc*, c-*fos*, c-*jun*, EGFr) and paraffin sections (p53; DO-7 antibody) were assessed by IHC The p53-positive areas were microdissected; the p53 gene was assessed by direct DNA sequencing of exons 4–9 in eight T1 tumours expressing c-*myc*. Apoptoses per 1000 malignant cells were counted in superficial TCC.

In superficial tumours, positive associations were detected between (1) IHC and flow cytometry; (2) cytoplasmic c-*myc* and either heterogeneous p53 staining ($P<0{\cdot}05$) or apoptosis ($P<0{\cdot}01$); (3) heterogeneous p53 staining and a non-mutated p53 gene; and (4) c-*jun* and EGFr staining ($P<0{\cdot}001$).

These findings are consistent with the hypothesis that c-*myc* is associated with upregulation of functional wild-type p53 and apoptosis in TCC.

Adenosine protects against interleukin-2-induced microvascular injury

K. Stokes, C. J. Kelly, G. Chen, H. P. Redmond, S. Sheehan, A. Tanner* and D. J. Bouchier-Hayes, *Royal College of Surgeons in Ireland, Departments of Surgery, Beaumont Hospital and *Meath Hospital, Dublin, Ireland*

Interleukin-2 (IL-2) is a potent antineoplastic agent, the use of which has been limited by an associated dose-dependent toxicity or the vascular leak syndrome This is due in part to leucocyte-mediated microvascular injury. The sequence of events in this injury are (1) a decrease in leucocyte rolling velocity, (2) leucocyte–endothelial adherence and finally (3) leucocyte transmigration to the interstitium. Adenosine *in vitro* inhibits neutrophil-mediated endothelial injury. The aim of this study was to assess the role of adenosine in preventing IL-2-induced leucocyte–endothelial interaction and leucocyte transmigration in the gut mesenteric vessels.

Intravital microscopy was used to calculate leucocyte rolling velocity, adherence and transmigration in single postcapillary venules (20–30 μm). Sprague–Dawley rats were randomized to saline and adenosine (2 μmol h^{-1} commencing 15 min before IL-2 administration) groups. All animals received $0{\cdot}5\times10^6$ units IL-2 intravenously. The number of leucocytes adhering and emigrating and the leucocyte rolling velocity were calculated at baseline and 30, 60, 90 and 120 min after IL-2 administration.

	Rolling velocity (μm s^{-1})		No. adherent (per 100 μm)		No. emigrated (per field)	
Time	IL-2	IL-2 + Ado	IL-2	IL-2 + Ado	IL-2	IL-2 + Ado
Baseline	40·6(3·0)	41·4(12·6)	3(0·7)	1(0·8)	1(0·6)	1(1·0)
30 min	33·3(1·6)	54·3(8·8)*	23(6·5)‡	4(2·7)	4(1·8)	2(1·5)
60 min	37·4(3·9)	51·9(10·6)	31(5·7)§	5(1·8)*	14(6·6)	1(0·3)
90 min	32·6(3·2)	62·6(19·6)	44(6·3)§	7(4·1)†	29(11·8)‡	1(0·7)
120 min	31·9(3·4)	48·4(18·5)	40(4·2)§	11(2·6)†	52(12·5)§	2(0·9)*

Data are mean(s.e.m.). Ado, adenosine. *$P<0{\cdot}05$, †$P<0{\cdot}01$ *versus* IL-2; ‡$P<0{\cdot}05$, §$P<0{\cdot}01$ *versus* baseline (analysis of variance with Scheffe post hoc correction)

In this model, IL-2 significantly increases leucocyte adherence and transmigration in the tissues. Adenosine increased leucocyte rolling velocity, reduced adherence and prevented the passage of activated leucocytes through the endothelial barrier. This agent, therefore has the potential to significantly limit the toxicity of IL-2 and may thus permit the use of higher dosages in cancer therapy.

Genetic diagnosis of lymph node metastases in patients with colorectal cancer

N. C. Marshall, E. Kinrade, D. Onwu, J. Van der Walt, N. S. Williams, S. A. Bustin and S. Dorudi, *Academic Surgical Department, Royal London Hospital, London, UK*

Lymph node involvement is an important determinant of prognosis in colorectal cancer but despite apparently curative surgery recurrence is a major problem and is the ultimate cause of death for 30 per cent of patients with node-negative tumours. Since adjuvant therapy may improve the prognosis it is important to identify these patients. This issue has been addressed by developing a sensitive genetic technique to re-stage patients undergoing surgery for cancer.

Lymph nodes were isolated from freshly resected specimens from 18 patients (range of node yield 2–26). One half of each node was prepared for conventional histopathology while the remainder was snap frozen in liquid nitrogen for immunocytochemistry and messenger RNA (mRNA) extraction. Use of a monoclonal antibody to the epithelial-specific cytokeratin CK20 confirmed the staging of three Dukes C tumours, but indicated no evidence of micrometastases in 12 patients with node-negative tumours. In contrast, use of the reverse transcription polymerase chain reaction (RT-PCR) resulted in the detection of additional lymph node involvement in two of the three patients with Dukes C disease as well as the genetic re-staging of two patients with histologically negative nodes. CK20 mRNA was not detected in 12 nodes obtained from three patients undergoing colorectal resection for benign conditions.

It is concluded that RT-PCR for CK20 mRNA is a sensitive technique for detecting viable epithelial (i.e. tumour) cells within lymph nodes. Further follow-up will be necessary but such genetic diagnosis should aid in establishing the prognosis and further treatment of patients undergoing 'curative' surgery for colorectal cancer.

Heat shock protein 70 causes the protection to tumour cells following heat shock from monocyte-mediated lysis

F. Campbell, H. P. Redmond, J. Harmey and D. Bouchier-Hayes, *Royal College of Surgeons in Ireland, Department of Surgery, Beaumont Hospital, Dublin, Ireland*

It has been well documented that tumour cells continue to proliferate despite the host producing tumoricidal mediators. This could be due to the induction of a protective heat shock response in the tumour cell. The authors have previously demonstrated that following induction of a heat shock response the colorectal cell line SW707 is protected from monocyte-mediated cell lysis. This was found not to be due to increased surface expression of heat shock proteins. The aim of this study was to assess whether intracellular heat shock protein (HSP) expression could cause this protective effect and to localize the site of expression. Toxicity of sodium arsenite (SA) to the cell at the doses and time point in question was also evaluated.

The heat shock response was induced by either SA (0–320 μmol l^{-1} for 6 h) or by hyperthermia (42°C for 30 min, followed by a 2-h recovery period). Whole cell lysates of treated cells were made and run on Western blots. Untreated cells were fractionated and samples run on Western blots. To assess the toxicity of SA, cells were grown on microtitre plates in the presence of SA for 6 h and the endpoint was assessed by crystal violet dye elution (CVDE). Statistics were by analysis of variance with Scheffe post hoc correction.

	HSP expression				6-h toxicity (CVDE) (optical density units)
	HSP27	HSP60	HSP70	HSP90	
Control	+	+	+	+	0·431(0·079)
SA 40 μmol l^{-1}	+	+	++	+	0·488(0·135)
SA 80 μmol l^{-1}	+	+	++	+	0·490(0·135)
SA 160 μmol l^{-1}	+	+	++	+	0·425(0·095)
SA 320 μmol l^{-1}	+	+	+	+	0·154(0·056)
42°C	+	+	++	+	

Values are mean(s.e.m.) for five experiments

The data indicate that expression of HSP70 but not of HSP27, HSP60 or HSP90 is increased following heat shock with all doses except 320 μmol l^{-1} SA; the latter dose also resulted in increased but non-significant toxicity to the cells. HSP70 was found to reside mainly in the cytoplasm in untreated cells. Although previous studies have demonstrated no increase in surface expression of HSP70 in treated cells, further work must be done on treated cells to assess whether HSP70 is translocated within the cell upon heat shock.

Neutrophil heat shock protein expression correlates with increased apoptosis following endothelial transmigration

S. Hennigan, J. H. Wang, H. P. Redmond and D. Bouchier-Hayes, *Royal College of Surgeons in Ireland, Department of Surgery, Beaumont Hospital, Dublin, Ireland*

Neutrophils (PMNs) undergo endothelial transmigration upon activation or in response to a chemoattractant. Such cells are stressed and have an increased capacity to incite tissue injury. Little is known about the effect of transmigration on PMN stress gene responses, PMN activation and, ultimately, apoptosis. The aim of this study was to evaluate the effect of PMN endothelial transmigration on stress gene responses and correlate this with activation state and apoptosis.

Human PMN transendothelial migration was examined using ECV 304 monolayers in which chemotaxis was induced by *N*-formyl-methionyl-leucyl-phenylalanine (fMLP). Heat shock protein (HSP72) expression was evaluated by Western immunoblotting, activation by CD11b, CD18 and phagocytosis and apoptosis by propidium iodide uptake and CD16.

	Control PMNs	Migrated PMNs
Apoptosis (%)		
4 h	6·0(1·0)	17·9(2·8)*
24 h	37·6(3·8)	61·4(6·3)*
Phagocytosis (MCF)	34·4(1·6)	95·8(23·8)*
CD11b (MCF)	790·1(77·3)	1694·4(293·2)*
CD16 (MCF)	493·2(118·8)	221·0(88·2)*
CD18 (MCF)	377·4(40·6)	851·3(105·0)*
HSP 72	+	+++

Values are mean(s.e.m.). MCF, mean channel fluorescence. *$P < 0·05$ *versus* control (*t* test)

Naive PMNs that migrate through endothelium in response to fMLP undergo activation. It has been shown for the first time that such cells are also programmed for increased HSP72 expression compared with controls which may serve to preferentially induce PMN apoptosis rather than necrosis, thus limiting tissue injury.

Peritoneal macrophage function in obstructive jaundice

C. Ryan, A. Kennedy, R. Parks, B. Rowlands and I. Halliday, *Department of Surgery, The Queen's University of Belfast, Belfast, UK*

Septic complications often follow invasive diagnostic and therapeutic procedures in patients with obstructive jaundice. This study investigates the role of altered peritoneal macrophage function in the development of these complications.

Male Wistar rats were randomized to control, sham and bile duct ligation (BDL). Three weeks after BDL peritoneal macrophages were harvested. In study 1 macrophages were stimulated with lipopolysaccharide (LPS) (*Escherichia coli* 0111:B4) in the presence of serum for 4 h. To investigate the refractory mechanism of these macrophages, in study 2 rats were given an intraperitoneal LPS injection (0·2 mg per 100 g) 2 h before harvesting the macrophages and performing LPS stimulation. Rat tumour necrosis factor (TNF) α in the supernatants was assayed by enzyme-linked immunosorbent assay and CD14 expression was analysed by flow cytometry.

	TNF (pg per μg DNA)				CD14 expression	
	Study 1		Study 2			
Group	No LPS	LPS 100 ng ml^{-1}	No LPS	LPS 100 ng ml^{-1}	% cells	MCF
Control	0·74(0·25)	7·94(0·56)	0·27(0·16)	0·19(0·09)	96·03	3·12
Sham	1·01(0·30)	16·08(1·87)†	0·26(0·09)	0·47(0·41)	96·20	3·37
BDL	2·89(0·76)*	30·67(3·42)*	0·51(0·32)	0·84(0·56)	97·03	3·35

Values are mean(s.d.) MCF, mean channel fluorescence. $^*P<0\cdot03$ *versus* sham or control both either with or without LPS; $^\dagger P<0\cdot03$ *versus* control + LPS (Mann–Whitney U test)

Peritoneal macrophages from animals with BDL have a greater secretory response than sham operated or control rats, both in the presence and absence of exogenous LPS, and can be termed hypersecretory. This activation cannot be explained by a failure of the macrophage refractory mechanism as the secretion of TNF was downregulated in all groups (study 2) or by an increase in CD14 expression. The exact mechanism for the upregulation of peritoneal macrophage function in obstructive jaundice remains to be elucidated.

Kupffer cell secretion of tumour necrosis factor is increased by prefeeding with L-arginine in obstructive jaundice

J. A. Kennedy, S. J. Kirk, W. D. B. Clements, G. R. Campbell, M. I. Halliday and B. J. Rowlands, *Department of Surgery, The Queen's University of Belfast, Belfast, UK*

L-Arginine (L-Arg) has beneficial immune effects in sepsis. Kupffer cells (KCs) contribute 85 per cent of total mononuclear cell function. Gram-negative sepsis and endotoxaemia are frequent events in obstructive jaundice. Accentuated mononuclear cell secretion of cytokines in response to lipopolysaccharide (LPS) may be a feature of sepsis-related complications in biliary obstruction. The effects of dietary supplementation with L-Arg on KC secretion of tumour necrosis factor (TNF) in obstructive jaundice were investigated.

Male Wistar rats ($n=40$, weight 250–300 g) were randomized to bile duct ligation (BDL) or sham operation and fed standard chow. Animals had free access to a solution of 1·8 per cent L-Arg (L-Arg diet) or water made isonitrogenous by the addition of glycine (control diet) and were studied on day 21. KC secretory response to LPS was assessed using single-pass *in situ* hepatic perfusion. Livers were perfused (30 ml min^{-1}) with buffer containing LPS (B4 0111; 1·6 μg ml^{-1}) for 10 min and for a subsequent 50 min with LPS-free perfusate. Effluent perfusate was assayed for TNF by enzyme-linked immunosorbent assay (ELISA) 60 min after exposure to LPS. Plasma was assayed for bilirubin, aspartate aminotransferase (AST) and TNF (ELISA).

There was no significant difference in plasma bilirubin, alkaline phosphatase or AST between animals receiving a control and L-Arg diet after BDL. TNF was not detected in plasma from sham or jaundiced animals in either dietary group but was present in effluent perfusate after 60 min in the following concentrations:

Group ($n=10$)	TNF (pg ml^{-1})	
	Control diet	L-Arg diet
Sham	87·9 (41·6–143·7)	69·6 (17·6–86·3)
BDL	793·0 (651·3–1185·5)*	1283·0 (1087·0–1788·5)*†

Values are median (interquartile range). $^*P<0\cdot05$ *versus* sham; $^\dagger P=0\cdot01$ *versus* BDL, control diet (Mann–Whitney U test)

Stimulated TNF was significantly greater in rats with BDL than sham operation in both dietary groups. Prefeeding with L-Arg enhanced KC secretion of TNF in response to endotoxin in animals after BDL. The immune stimulating actions of L-Arg may include increased KC secretory responses to septic stimuli in experimental obstructive jaundice.

Are colorectal carcinomas angiogenesis dependent?

C. RoshanLall, G. O'Dowd*, D. Lowe, A. Kinsella and J. R. H. Winstanley, *University Departments of Surgery and *Pathology, Royal Liverpool Hospital, Liverpool, UK*

It has been suggested that the growth and maintenance of solid tumours are dependent on the potential of tumour cells to induce angiogenesis in the host stroma. Tumour angiogenesis is quantified by microvessel density (MVD). However, there are conflicting reports on the role of angiogenesis in colorectal cancer. MVD was quantified in the invasive tumour and in the corresponding uninvolved mucosa in 50 primary colorectal adenocarcinomas.

The criterion for selection of tissue blocks was presence of representative tumour with an invasive edge and uninvolved mucosa, both adjacent to and distant from the tumour periphery (TP). Sections of 4 μm were cut from routinely processed paraffin blocks and stained with the monoclonal antibody QB/end/10, using the ABC immunohistochemical technique, following predigestion with trypsin. QB/end/10 is generally accepted to be the optimal immunohistochemical marker for endothelial cells. Individual microvessel counts were made in ten 400× fields (40× objective and 10× ocular), by two independent observers, in the tumour centre (TC), TP, tumour-free colonic mucosa immediately adjacent to the tumour (MA), and in normal colon at a distance of at least 2 cm from the TP (N).

	TC	TP	MA	N
Mean(s.d.) MVD	8·1(4·0)	10·3(4·5)	22·8(11·0)	26·5(10·6)

MVD of the MA did not differ significantly from that in normal colon ($P=0\cdot15$, paired t test). These values were however, significantly higher than the MVD in the periphery or centre of the tumour ($P<0\cdot0001$). No localized increases in tumour microvessels ('hotspots') were identifed in the TP.

The results of this study suggest that MVD is decreased in the TP when compared with corresponding uninvolved mucosa. Therefore, unlike in other solid cancers, angiogenesis may not have a role in colorectal carcinomas.

Spermine/spermidine changes in inflammatory bowel disease

Y. Z. Almallah, K. M. Nicoll, N. A. G. Mowat, T. S. Sinclair, S. D. Heys, O. Eremin and H. M. Wallace, *Departments of Surgery, Medicine and Therapeutics and Biomedical Sciences, University of Aberdeen, and Gastrointestinal Unit, Aberdeen Royal Infirmary, Aberdeen, UK*

Polyamines (PAs) are naturally occurring aliphatic polycations whose distribution in tissues and body fluids is increased in inflammatory conditions. It is believed that increased availability of PAs in tissues enhances inflammation whilst resolution is associated with increased elimination of PAs. Animal studies show that PA deprivation (dietary and enzyme inhibitors) suppresses cell growth and metabolism. An important route of elimination of PA from tissues, especially the gut, is the sequestration of PAs into red blood cells (RBCs). The aim of this study, therefore, was to establish the RBC PA level in patients with inflammatory bowel disease (IBD) and to investigate the changes in these levels following therapy.

Blood samples (4·5 ml) were collected, and RBCs were isolated, washed in saline and haemolysed in distilled water. PAs were extracted with hydrochloric acid 1 mol l^{-1} and measured fluorometrically by high-performance liquid chromatography. In the first phase of the study, patients with active IBD ($n = 24$) had significantly higher RBC PA concentrations compared with age- and sex-matched healthy controls ($n = 8$): median (range) spermidine 0·93 (0·14–2·65) nmol per ml blood and spermine 0·79 (0·13–4·22) nmol ml^{-1} *versus* 0·17 (0·09–0·23) and 0·07 (0·03–0·12) nmol ml^{-1} respectively ($P < 0·001$, Mann–Whitney U test)

In the second phase of the study, RBC PAs were monitored in patients undergoing treatment ($n = 18$). Patients were evaluated every month for 6 months using clinical and sigmoidoscopic scores Those who went into remission ($n = 13$), had a significantly progressive increase in RBC PA content between months 2 and 6 compared with baseline values ($P < 0·05$, Wilcoxon pairs) Further investigations are ongoing to delineate more fully the metabolism of PAs in the pathogenesis of IBD.

Endothelin-1 production and secretion by colorectal cancer

A. Shankar, M. Loizidou, S. Frederick*, G. Aliev†, D. W. Holt*, G. Burnstock†, P. Boulos and I. Taylor, *Department of Surgery, University College London Medical School, *The Analytical Unit, St George's Hospital Medical School and †Department of Anatomy, University College London, London, UK*

Endothelin-1 (ET-1), a vasoconstrictor peptide, has been implicated as a tumour growth stimulator. To assess its importance in colorectal cancer, immunoelectron microscopy (EM) for ET-1 was performed on colorectal liver metastases and normal hepatic tissue ($n = 8$). In addition, plasma levels of both ET-1 and thrombomodulin, a marker of endothelial damage, were measured in patients with colorectal cancer, with and without liver metastases, and compared with an age- and sex-matched control group.

EM of the normal liver showed poor staining for ET-1 in endothelial cells, whilst endothelium, tumour cell nests and surrounding myofibroblasts within the tumour stained densely. Mean(s.d.) plasma level of ET-1 in the control group ($n = 22$) was 2·6 (1·25) pg ml^{-1}. Plasma levels of ET-1 were raised in 15 patients with colorectal liver metastases (4·6 (1·75) pg ml^{-1}, $P < 0·001$) and in 11 without metastases (3·8 (1·14) pg ml^{-1}, $P = 0·02$) Thrombomodulin levels were similar in all groups, indicating that changes in ET-1 levels were not due to damaged endothelium.

These results indicate that primary colorectal cancer and colorectal liver metastases produce ET-1. ET-1 may modulate tumour vascular tone or act as a direct growth stimulator.

Lectin binding is a predictor of poor survival in patients with colorectal cancer

P. Gandhi, P. B. Boulos, S. Brooks, V. Sams*, U. M. Weisgerber and A. Leathem, *Departments of Surgery and *Histopathology, University College London Medical School, London, UK*

The relationship between tumour binding of the lectin Helix Pomatia agglutinin (HPA) and prognosis has been well documented in several human carcinomas but not in colorectal carcinoma. Its sugar specificity makes it an excellent tool in investigation of the minor glycosylation changes known to occur in the metastatic cell HPA binding has therefore been evaluated as a predictor of survival in 120 patients (Dukes A, $n = 17$; Dukes B, $n = 62$; Dukes C, $n = 41$) with 10-year clinical follow-up who underwent curative resection for colorectal cancer between 1983 and 1985.

Sections from formalin-fixed paraffin wax-embedded blocks were stained for HPA binding using the indirect immunoperoxidase method. They were graded by two independent observers as either positive or negative stainers; positive stainers were those in which at least 5 per cent of tumour cells stained strongly or 50 per cent of tumour cells stained weakly.

Kaplan–Meier survival curves revealed a significant difference in survival between positive and negative stainers ($\chi^2 = 35·1$, $P < 0·0001$). Risk estimates were obtained in a multivariate Cox's proportional hazards model. The relative hazard of HPA positive staining *versus* negative staining was 4·79 (range 2·85–8·04) and remained essentially unchanged at 4·31 (range 1·99–9·35) when adjusted for Dukes stage.

These results indicate that HPA binding is a highly significant and independent predictor of poor survival in patients with colorectal cancer and could be used to identify a high-risk group for careful surveillance.

Replication errors in colorectal cancer: correlation with family history

S. R. Brown, L. Cawkwell, P. J. Finan, N. R. Hall, G. R. Taylor and D. T. Bishop, *ICRF Genetic Epidemiology Department and Centre for Digestive Diseases, Leeds General Infirmary, Leeds, UK*

Replication errors (RERs) characterize a proportion of colorectal cancers, particularly those from genetically predisposed (hereditary non-polyposis colorectal cancer, HNPCC) patients. The Amsterdam criteria define families on the basis of family history who are likely to have the germline defect seen in HNPCC. However, familial clustering of cancers is often seen in families who do not meet the Amsterdam criteria Using a fluorescent polymerase chain reaction with microsatellites at up to seven loci the incidence of RERs in patients with varying strength of family history of bowel cancer was studied.

Three of three patients from HNPCC families with a known mutation were RER positive. A further five of 11 patients from families, many only just meeting the Amsterdam criteria, were RER positive. In contrast only one of 11 patients with two affected first-degree relatives and one of 20 with one affected first-degree relative were RER positive. Only one of a group of six patients with early-onset (less than 50 years) cancer with no family history was RER positive. In 75 per cent of all RER-positive tumours, the tumour was right sided.

These data indicate that RERs are a feature of tumours from HNPCC families, especially those meeting the Amsterdam criteria, but occur infrequently in families with a less strong family history and in left-sided tumours

Mucosal substrate utilization in Crohn's disease

M. C. Regan, M. M. Duffy, M. G. Harrington and P. R. O'Connell, *Departments of Surgery and Biochemistry, Mater Misericordiae Hospital and University College Dublin, Dublin, Ireland*

Alteration in colonic butyrate metabolism has been reported in ulcerative colitis (UC). To determine whether similar changes occur in Crohn's colitis, endoscopic biopsy samples of colonic and ileal mucosa were obtained from patients with documented Crohn's colitis, UC and control patients. Using a microculture technique, biopsy utilization of [^{14}C] glutamine and [^{14}C] butyrate was measured as [^{14}C]carbon dioxide production, trapped in a closed culture system. All assays were performed in duplicate. Biopsy size was determined as DNA content, using the Hoechst dye technique.

Butyrate metabolism was reduced in UC colonic mucosa (mean(s.e.m.) 0·90(0·22) pmol per μg DNA per h, $n = 10$) and Crohn's colonic mucosa (1·35(0·26) pmol per μg DNA per h, $n = 10$) compared with that in normal colonic mucosa (2·34(0·40) pmol per μg DNA per h, $n = 10$; $P < 0{\cdot}05$, analysis of variance). Glutamine metabolism was likewise reduced in both UC colonic mucosa (mean(s.e.m.) 0·06(0·01) pmol per μg DNA per h, $n = 10$) and Crohn's colonic mucosa (0·11(0·02) pmol per μg DNA per h, $n = 10$) compared with that in normal colonic mucosa (0·19(0·01) pmol per μg DNA per h, $n = 10$; $P < 0{\cdot}05$). There were no significant differences in ileal glutamine or butyrate metabolism in patients with either UC or Crohn's disease. It is concluded that the alteration in colonic mucosal metabolism observed in UC is a consequence of the inflammatory process and is not peculiar to UC. Ileal mucosal metabolism is unchanged in both UC and Crohn's disease, indicating that there is no panenteric metabolic abnormality.

Intravenous short-chain fatty acids and catheter infection in the rat total parenteral nutrition model

H. F. McAndrew, H. K. F. van Saene, R. J. Rintala and D. A. Lloyd, *Departments of Child Health and Microbiology, University of Liverpool, Liverpool, UK*

Catheter infection is a major cause of mortality and morbidity in patients receiving total parenteral nutrition (TPN). Gut mucosal atrophy occurs in rats receiving TPN and may predispose to bacterial translocation and catheter infection. Short-chain fatty acids (SCFA) have a trophic effect on the gut mucosa and may ameliorate translocation. The effect of supplemental SCFA on bacterial translocation and catheter infection in rats receiving TPN was therefore investigated.

Aseptic technique was used for silastic central venous catheter insertion and administration of intravenous feeds to Wistar rats. Group 1 received standard TPN and no enteral feed; group 2, TPN with SCFA and no enteral feed; group 3, intravenous saline with free access to standard chow, and group 4, no central line with free access to standard laboratory chow. Rats were sacrificed after 1 week on their diet. Mesenteric lymph nodes (MLN), liver, spleen, blood and the catheter were cultured. χ^2 by Pearson's or Fisher's two-tailed exact test was used for analysis.

	Number of positive cultures					
Group	MLN	Spleen	Liver	Portal blood	Cardiac blood	Catheter
1 ($n = 15$)	12	7	5	5	6	7
2 ($n = 14$)	7	6	7	4	4	1
3 ($n = 14$)	2*	1*	1*	2*	3*	5
4 ($n = 12$)	0*	0*	0*	0*	0*	—

*$P < 0{\cdot}05$ *versus* group 1

There was significant translocation in rats receiving TPN compared with that in both control groups, but no significant increase in catheter infection ($P = 0{\cdot}55$, group 1 *versus* group 3). Supplemental SCFA reduced translocation, but not significantly; however, the incidence of catheter infection was significantly reduced compared with that in animals receiving TPN only ($P < 0{\cdot}05$). It is concluded that SCFA supplementation of TPN reduces catheter infection.

Laparoscopy promotes intraperitoneal tumour growth in an animal model

H. R. Dorrance, K. Oein* and P. J. O'Dwyer, *University Departments of Surgery and *Pathology, Western Infirmary, Glasgow, UK*

The effect of laparoscopy on cancer spread is poorly understood. The aim of this study was to assess the effect of carbon dioxide and helium pneumoperitoneum on tumour growth and metastasis in an animal model. Under general anaesthesia and in separate experiments female F344 rats were given an intraperitoneal or tail vein injection of 1×10^5 Mtln$_3$ tumour cells and then randomized into three groups: anaesthetic only (control), carbon dioxide pneumoperitoneum and helium pneumoperitoneum. Insufflation pressure was 8 mmHg

Group	No.	Omental tumour (g)	Peritoneal nodules
Control	20	4·0 (3·2–5·9)	0 (0–1·0)
Carbon dioxide	20	7·5 (5·8–8·8)	17·0 (10·0–20·0)
Helium	20	6·1 (5·0–8·3)	19·5 (12·5–25·7)
*P**		0·018	0·0001

Values are median (interquartile range). *Compared with controls (Mann–Whitney *U* test)

Following tail vein injection of Mtln$_3$ tumour cells, lung metastases occurred with equal frequency in control and insufflated groups: control median (interquartile range) 5 (3–12); carbon dioxide 9 (7–10); helium 6 (6–14) (*P* not significant).

This study shows that laparoscopy promotes intraperitoneal tumour growth and spread but has no effect on distant metastasis. This effect is independent of the gas used and appears to be a result of tumour dissemination by insufflation.

Thermal preconditioning (thermotolerance) protects against leucocyte–endothelial interactions *in vivo*

G. Chen, C. Kelly, K. Stokes, J. Wang, A. Tanner* and D. J. Bouchier-Hayes, *Royal College of Surgeons in Ireland, Departments of Surgery, Beaumont Hospital and *Meath Hospital, Dublin, Ireland*

The clinical use of interleukin-2 (IL-2) has been limited by a leucocyte-mediated endothelial injury, known as the vascular leak syndrome (VLS). Leucocyte adherence and migration are critical events in the development of VLS. Exposure of cells to a subcritical stress, such as hyperthermia (thermotolerance), may protect cells from subsequent injury, possibly by inducing heat shock protein (HSP) expression. However, the role of thermotolerance in decreasing VLS is unknown. The present study investigated the effect of thermotolerance on leucocyte adherence and migration induced by IL-2 in rat mesenteric postcapillary venules (20–35 μm).

Sprague–Dawley rats were randomized to IL-2 only and thermotolerance + IL-2 (T + IL-2) groups. Thermotolerance (raising core body temperature to 41 ± 0·5°C for 15 min) was induced 18 h before IL-2 administration (1×10^6 units per rat). The number of adherent and migrated leucocytes, and their rolling velocity, were measured by intravital microscopy at baseline (0 min), and 30 and 60 min after IL-2 injection. HSP72 expression in lung, intestine and mesentery was determined by Western immunoblotting.

	No adherent (per 100 μm)		No migrated (per field)		Rolling velocity (μm s^{-1})	
	IL-2	T + IL-2	IL-2	T + IL-2	IL-2	T + IL-2
0 min	2·7(0·42)	1·3(0·33)	1·5(0·56)	0·5(0·34)	41·3(4·49)	50·9(1·62)
30 min	10·5(2·99)†	1·8(0·40)*	6·5(2·00)†	1·5(0·34)*	32·5(1·17)	47·5(1·98)*
60 min	18·2(5·12)†	3·0(0·37)*†	16·7(6·08)†	3·2(0·79)*†	32·6(2·60)	46·7(2·33)*

Values are mean(s.e.m.) $^*P<0\cdot05$ *versus* IL-2 only; $^\dagger P<0\cdot05$ *versus* 0 min (unpaired Student's *t* test)

In this model, IL-2 significantly increased leucocyte adherence and migration, and decreased leucocyte rolling velocity at 30 and 60 min. Thermotolerance prevented IL-2-induced increases in leucocyte adherence and migration, and the decrease in leucocyte rolling velocity. This was associated with an increase in HSP72 expression in the lung, intestine and mesentery compared with that seen with IL-2 alone. This study demonstrates that thermotolerance inhibits leucocyte–endothelial interactions possibly by increasing expression of HSP72 in tissues, suggesting a role for thermotolerance in treating leucocyte-mediated microvascular injury.

How evidence-based is general surgery (and does it matter?)

N. Howes, L. Chagla, M. Thorpe and P. McCulloch, *Aintree Hospitals National Health Service Trust and Department of Surgery, University of Liverpool, Liverpool, UK*

There is considerable current interest in the concept of evidence-based clinical practice. Our subjective impression was that fewer 'surgical' than 'medical' interventions are supported by evidence from randomized controlled trials (RCTs). A study was therefore conducted to determine the extent to which current surgical practice is evidence-based.

Over a 1-month period all overnight admissions to one surgical firm were audited prospectively, and the main therapeutic intervention classified by a panel of eight junior and senior surgical staff as (1) supported by RCT evidence, (2) supported by strong enough non-RCT evidence to make a placebo-controlled trial unethical or (3) neither. The results are shown in the *Table*

	Category 1	Category 2	Category 3	Total
Elective cases	18	26	0	44
Emergency cases (with operation)	13	9	0	22
Emergency cases (no operation)	2	27	5	34
Total	33	62	5	100

Overall 95 per cent of surgical interventions are evidence-based, but only 33 per cent are based on evidence from RCTs. No significant differences were found between emergency and elective or between operative and non-operative interventions. In hospital medicine 82 per cent of interventions are evidence-based and 53 per cent are based on evidence from RCTs. Many surgical problems are inherently difficult to subject to RCT. Current methods of classification of evidence fail to reflect the wide variation in the quality of non-RCT evidence, and require refinement.

Comparison of general practitioner and surgical evaluation of emergency surgical admissions

P. McCulloch, J. Bowyer, R. Ward, T. Fitzsimmons and D. Lowe, *Department of Surgery, University of Liverpool and Aintree Hospitals National Health Service Trust, Liverpool, UK*

General surgical units have experienced a 20 per cent rise in emergency admissions in recent years, diminishing their elective capacity. Several commentators have suggested that the general practitioner (GP) threshold for seeking emergency admission may have decreased in the reorganized National Health Service. A prospective study was performed to determine the percentage of emergency admissions judged unnecessary on clinical grounds by surgeons and GPs. A 6-month prospective audit of general surgical emergency admissions was carried out. For 50 randomly selected cases, summaries were prepared and assessed independently by three groups: (1) ten local GPs, (2) ten junior surgical staff members and (3) an 'expert panel' of two consultant surgeons and one GP. Cases were scored as (A) definitely requiring admission, (B) unclear whether admission appropriate or (C) admission definitely inappropriate. The results are shown in the *Table*.

	No. of cases		
	A	B	C
Surgical staff	28	12	10
Expert panel	32	14	4
GPs	21	13	16

Between 8 and 32 per cent of the admissions were considered unnecessary by the three groups. Agreement was moderate between surgical junior staff and the expert panel (Kappa = 0·43) but poor between experts and GPs (Kappa = 0·18). GPs were consistently less willing than the experts to admit patients. These results refute the belief that GPs seek to admit as emergencies cases that are considered unjustified by experienced surgical staff.

Free radical blockade and ureteric obstruction

P. Downey, M. Young, S. R. Johnston and B. J. Rowlands, *Department of Surgery, The Queen's University of Belfast, Belfast, UK*

The authors have recently shown that the release of ureteric obstruction is associated with free radical production and ipsilateral reduction in renal blood flow (RBF). This study assessed the effect of allopurinol on RBF following release of ureteric obstruction.

In a porcine model, a flow probe was inserted around the left renal artery; the left ureter was divided, the distal segment ligated and a Ch 9 tube passed retrogradely into the renal pelvis forming a ureterostomy. A Swan–Ganz catheter was placed in the left renal vein. Following recovery for 24 h baseline RBF was recorded for 2 h. Subsequently an obstructed group ($n = 6$) underwent 6 h of ureterostomal occlusion followed by release. A control group ($n = 6$) did not undergo ureterostomal occlusion. The effect of allopurinol (400 mg intravenously after 2 h of baseline recording) on RBF was assessed in two additional groups: Control + All ($n = 6$) and Obstructed + All ($n = 6$). Evidence of free radical production was assessed in renal venous samples using the Fox assay for lipid peroxidation. Mean RBF for 4 h following release of obstruction and Fox assay concentrations 2 h after release of obstruction were calculated and expressed as percentage change from baseline values.

Group	Change in RBF (%)	Change in Fox assay (%)
Control	5·3(2·6)	−9·2(0·5)
Obstructed	−16·0(2·8)*	22·7(8·0)*
Control + All	3·2(2·0)	−4·2(3·7)
Obstructed + All	0·7(2·7)†	3·8(2·3)

Values are mean(s.d.). *$P = 0{\cdot}002$ *versus* control; †$P = 0{\cdot}02$ *versus* obstructed (Mann–Whitney U test)

In the obstructed group increased free radical production was associated with a significant reduction in RBF. Pretreatment with allopurinol eliminated these changes; allopurinol may be a useful therapeutic agent in the management of ureteric calculus disease.

Mechanisms of apoptosis in pancreatic cancer cell lines

J. D. Evans, S. R. Bramhall, J. P. Neoptolemos and M. C. Eggo*, *Departments of Surgery and *Medicine, Queen Elizabeth Hospital, Birmingham, UK*

The growth and progression of cancer may involve both an increase in cell proliferation and a reduction in apoptosis (programmed cell death). Protein kinase C (PKC) is a serine–threonine kinase which has an important role in cell proliferation and survival including the control of apoptosis.

Pancreatic cancer cell lines (SUIT 2 and BXPC3) grown in serum-free conditions were treated for 24 h with indomethacin, which inhibits the cyclo-oxygenase pathway, and the tumour promoting phorbol esters 12-0-tetradecanoylphorbol-13-acetate (TPA) and 12-deoxyphorbol-13-0-phenylacetate-20-acetate (DOPPA), which activate PKC. Cell proliferation was assessed by the incorporation of $[^3H]$thymidine. DNA laddering was used to assess apoptosis.

Treatment of SUIT 2 and BXPC3 pancreatic cancer cell lines with TPA, a pan activator of PKC isoenzymes, inhibited cell proliferation in a dose-dependent manner and induced apoptosis ($P < 0{\cdot}02$, one sample t test). DOPPA, which only activates the β_1 isoform of PKC, produced a similar effect. Indomethacin did not inhibit the proliferation of cell lines or induce apoptosis.

TPA (ng ml^{-1})	Change in incorporation of $[^3H]$thymidine (%) SUIT 2	BXPC3
0	0	0
10^{-9}	−40·2 (−36·6 to −44·7)	−12·3 (−2·8 to −29·0)
10^{-8}	−63·6 (−60·6 to −67·6)	−41·1 (−28·9 to −48·4)
3×10^{-8}	−75·5 (−70·0 to −78·2)	−54·4 (−49·6 to −59·2)
10^{-7}	−80·3 (−79·6 to −81·7)	−52·5 (−49·6 to −55·6)
3×10^{-7}	−82·2 (−81·2 to −84·4)	−54·7 (−47·8 to −62·6)

Values in parentheses are ranges

Phorbol esters inhibit the proliferation and induce apoptosis of pancreatic cancer cell lines. This effect appears to be mediated by the β_1 isoform of PKC. A greater understanding of mechanisms of apoptosis may enable the development of new therapeutic strategies in the future.

Does enteral feeding in acute pancreatitis preserve total antioxidant potential?

S. Kanwar, A. C. J. Windsor, J. I. Spark, F. K. S. Welsh, A. Li, L. Gallivan, P. J. Guillou and J. V. Reynolds, *Academic Unit of Surgery, St James's University Hospital, Leeds, UK*

Oxygen free radicals (OFRs) are considered key mediators of local and remote tissue injury in acute pancreatitis. In critically ill patients a balance exists between the destructive potential of OFRs and protective effects of serum antioxidants. Systemic endotoxaemia resulting from gut barrier failure increases oxidant stress, tipping this balance in favour of tissue injury. This study examined the hypothesis that feeding the gut in acute pancreatitis may, by preserving gut barrier function, limit endotoxin exposure and oxidant stress, thus reducing organ injury while maintaining antioxidant potential.

Sixteen patients with acute pancreatitis were randomized to receive either enteral or parenteral nutrition and were monitored for evidence of organ failure. Patients' sera were measured for total antioxidant potential and immunoglobulin (Ig) M antiendotoxin antibodies (EndoCAb) before and after 7 days of nutritional support.

The *Table* shows number of organs failed and percentage change from prenutritional values for EndoCAb and antioxidant potential:

Nutrition	No. of organs failed	Change in EndoCAb (%)	Change in antioxidant potential (%)
Enteral	0	−0·02*	33*
Parenteral	3	74	−28

*$P < 0{\cdot}05$ *versus* parenteral nutrition (Mann–Whitney U test)

These data demonstrate that feeding the gut in acute pancreatitis reduces the IgM antibody response to endotoxin indicating a reduced recent exposure to endotoxin. In those fed enterally the total antioxidant potential was significantly increased compared with that in the parenterally fed group indicating reduced OFR activity. Reduced endotoxaemia and oxidant stress are manifest by a clinical improvement in terms of remote organ injury. Thus, feeding rather than conventionally resting the gut may significantly benefit clinical outcome in acute pancreatitis.

Serosal fibroblasts promote stricture formation in Crohn's disease

B. M. Flavin, M. C. Regan, J. M. Fitzpatrick and P. R. O'Connell, *Department of Surgery, Mater Misericordiae Hospital, Dublin, Ireland*

The aim of this study was to determine whether serosal fibroblasts in patients with Crohn's disease have an inherently enhanced capacity to reorganize collagen and cause scar contraction.

Fibroblasts, obtained at surgery, from normal and Crohn's colon and ileum were cultured by an explant technique. Fibroblast contractile activity was measured using fibroblast populated collagen lattices, in which cultured fibroblasts are seeded in free floating collagen gel matrices, which they reorganize and contract. The fibroblast contractile activity was measured at 24-h intervals, as reduction of the surface area of collagen gel matrix.

	n	Surface area (mm^2) 24 h	48 h	72 h	96 h	120 h
Normal colon	25	824(33)	698(42)	579(53)	393(40)	301(36)
Crohn's colon	9	613(64)*	484(62)*	320(39)*	222(18)*	146(11)*
Normal ileum	10	952(11)	766(80)	649(90)	552(106)	518(109)
Crohn's ileum	17	586(44)†	489(38)†	373(27)†	308(24)†	274(26)†

Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* normal colon; †$P < 0{\cdot}05$ *versus* normal ileum (analysis of variance)

These data show that serosal fibroblasts recovered from both colon and ileum of patients with Crohn's disease possess an inherently enhanced capacity for collagen reorganization and contractile activity *in vitro*. Such activity may be responsible for stricture formation in Crohn's disease.

Impaired gut barrier function in protein malnourished patients

F. K. S. Welsh, C. W. Ramsden, G. R. Barclay*, P. J. Guillou and J. V. Reynolds, *Academic Unit of Surgery, St James's University Hospital, Leeds and *Blood Donor Centre, Edinburgh, UK*

The integrity of the gastrointestinal mucosa is a key element in preventing systemic absorption of enteric toxins and bacteria. In the critically ill, breakdown of gut barrier function may fuel sepsis. Patients with protein–calorie malnutrition have an increased risk of postoperative sepsis; the effects of malnutrition on intestinal barrier function in humans however, are unknown. The aim of this study was to quantify intestinal barrier function, endotoxin exposure and the acute phase cytokine response in malnourished surgical patients.

Gastrointestinal permeability was measured in 14 malnourished patients and 16 well-nourished controls using the lactulose–mannitol test The immunoglobulin (Ig) G antibody response to endotoxin (antiendotoxin core antibody, EndoCAb), which is an indirect measure of endotoxin exposure, and serum interleukin-6 (IL-6) were determined by enzyme-linked immunosorbent assay.

	Controls	Malnourished patients
Plasma albumin (g l^{-1})	42 (39–44)	33 (32–38)†
Lactulose·mannitol ratio	0·03 (0·01–0·06)	0·15 (0·09–0·72)*
IgG EndoCAb (MU ml^{-1})	112 (48–184)	144 (74–253)
IL-6 (pg ml^{-1})	3 (<3–5)	8 (4–23)†

Values are median (interquartile range). *$P<0·01$, †$P<0·05$ *versus* controls (Mann–Whitney U test)

There was a significant increase in intestinal permeability in the malnourished group in association with raised IL-6 but no evidence of increased endotoxin exposure.

These data demonstrate that intestinal barrier function is significantly compromised in protein malnourished patients, although the clinical significance is as yet unclear. The use of permeability studies to monitor the efficacy of nutritional therapies in restoring gut function may have a sound rationale.

Expression of vascular endothelial growth factor in the primary tumours and sera of patients with pancreatic cancer

R. F. Hastie, D. F. Baban*, J. D. Evans, N. K. Green, S. R. Bramhall, J. P. Neoptolemos and L. W. Seymour*, *Department of Surgery and *Cancer Research Campaign Institute for Cancer Studies, University of Birmingham, Birmingham, UK*

Vascular endothelial growth factor (VEGF) is a 34–42 kDa heparin-binding growth factor important in wound healing and in various pathological states, including many cancers It mediates a range of paracrine activities via specific receptors on vascular endothelial cells, most notably influencing angiogenesis and vascular permeability. In the normal adult VEGF is expressed at high levels only during the menstrual cycle; hence in VEGF-secreting tumours it represents a novel, accessible and potentially tumour-selective target for therapeutic intervention.

In this study the expression of VEGF in pancreatic carcinoma was investigated. VEGF isoform expression was determined by reverse transcription–polymerase chain reaction (RT–PCR) of tumour biopsy samples and levels of VEGF protein were measured in preoperative serum of patients, using an enzyme-linked immunosorbent assay technique. Five of 12 pancreatic carcinoma tumour biopsies were found to express VEGF by RT-PCR, with 121, 165 and 189 amino-acid isoforms mainly coexpressed. Six of six biopsy samples of normal pancreatic tissue failed to indicate expression of VEGF. The results of serum analysis showed a mean(s.d.) level of VEGF expression in ten normal volunteers of 187(144) pg ml^{-1}. It is notable that ten of 20 patients with stage 4 carcinoma had a serum VEGF level more than three standard deviations above the normal mean (greater than 619 pg ml^{-1}), although four of 20 had a concentration of less than 100 pg ml^{-1}. In addition, all individuals examined with a serum VEGF level in excess of 619 pg ml^{-1} had either stage 3 or 4 carcinoma.

The results indicate that VEGF is expressed and secreted by a major fraction of pancreatic carcinomas, although there are clearly some advanced tumours that are VEGF negative. This allows classification of pancreatic carcinomas by VEGF expression and could reflect different pathophysiology. High expression of VEGF in pancreatic cancers may provide a useful opportunity for selective therapeutic intervention, either by receptor antagonism, by inhibition of endothelial signalling or by exploiting selective activation of the VEGF promoter for tumour-specific expression of exogenously administered therapeutic genes.

Ethanol interacts with the cholecystokinin receptor and causes calcium release from intracellular pools in mouse pancreatic acinar cells

J. B. Ward, R. Sutton and O. H. Petersen, *Department of Surgery and the Physiological Laboratory, University of Liverpool, Liverpool, UK*

Alcohol is an important cause of acute pancreatitis. As abnormal calcium homoeostasis may be implicated in acute pancreatitis, this study examined the direct effects of ethanol on acinar cell calcium ($[\mathrm{Ca}^{2+}]_i$) signalling.

Pancreases were excised from male CD1 mice and acini were isolated by collagenase digestion. Cells were loaded with fura-2 and $[\mathrm{Ca}^{2+}]_i$ signalling was studied by means of digital imaging microfluorimetry Experiments were carried out in Ca^{2+}-free medium.

On perfusion of 200 mmol l^{-1} ethanol, 17 (26 per cent) of 66 cells demonstrated an increase in $[\mathrm{Ca}^{2+}]_i$ of greater than 100 nmol l^{-1}. In these cells the mean(s e.m.) amplitude of increase was 552(75·3) nmol l^{-1}. Some 30 of 40 responded to 600 nmol l^{-1} with an amplitude of 491(39·6) nmol l^{-1}. Perfusion of cells with 2 μmol l^{-1} thapsigargin following 10 min of stimulation with 600 mmol l^{-1} ethanol demonstrated a significantly diminished increase in $[\mathrm{Ca}^{2+}]_i$ (amplitude 21(4·6 nmol l^{-1}) compared with controls 467(26·9) nmol l^{-1}; $P=0·0001$, Mann–Whitney U test).

Five minutes of perfusion with ethanol produced a dose-dependent increase in the delay of initiation of $[\mathrm{Ca}^{2+}]_i$ increase upon subsequent application of 100 pmol l^{-1} cholecystokinin (CCK) (control 9·6(0·64) s *versus* 200 mmol l^{-1} ethanol 27 0(1 81) s, $P=0\ 0001$, *versus* 600 mmol l^{-1} ethanol 40·3(3·63) s, $P=0·0001$) There was no such progressive delay with acetylcholine or bombesin.

These data indicate that ethanol may initiate Ca^{2+} release from thapsigargin-sensitive intracellular stores, possibly by interaction with the CCK receptor. As supramaximal stimulation by CCK is known to induce acute pancreatitis, these effects could be important in the pathogenesis of the disease.

Stool DNA yield and the detection of K-*ras* mutations in patients with colorectal cancer using the amplification refractory mutation system

N. R. Cruickshank, G. Ellison*, N.R. Charlesworth*, J. C. Fox*, A. Jones†, R. Cobb†, D. Morton and J. P. Neoptolemos, *Department of Surgery, Queen Elizabeth Hospital, Birmingham, †Cancer Diagnostics Research and Development, Zeneca Diagnostics and *Birmingham Heartlands NHS Trust, Birmingham, UK*

Molecular analysis of stool DNA has the potential of providing a non-invasive screening test for colorectal neoplasia. This study evaluated the extraction of human DNA from stool combined with the identification of K-*ras* mutations using the amplification refractory mutation system (ARMS).

Some 35 consecutive matched stool and tumour samples were analysed. Stool samples were collected on admission to hospital before surgery, 2–4 g of stool being used in each silica-based DNA extraction. The human DNA extracted from stool was evaluated by serial dilution and polymerase chain reaction (PCR) amplification using three common human-specific primer sequences: exons 1 of the cystic fibrosis, α_1-antitrypsin and K-*ras* genes. Tumour DNA and matched stool DNA were then evaluated using ARMS allele-specific amplification for seven common K-*ras* common mutations in codons 12 and 13.

Human DNA was isolated in 32 of 35 stool samples and quantified by serial dilution and PCR amplification (dilution range from 1 in 5 to 1 in 1000). Of 35 tumours 13 were K-*ras* positive and the corresponding mutation was identified in seven of 13 stool samples, with no false positives. In the K-*ras*-positive stool samples six of seven stool samples had a stool DNA quality greater than one in 200; correspondingly only one in seven samples with a stool dilution of less than 1 in 50 had the tumour mutation identified ($2P = 0{\cdot}0047$, Fisher's exact probability test).

These results suggest that DNA yield is essential to successful stool DNA mutational analysis. In the presence of a high DNA yield from stool, molecular analysis can provide a sensitive and specific test for colorectal cancer, but progress with this novel screening method will be dependent on developing improved extraction techniques

Apoptosis, p53 and Bcl-2 expression and prognosis in colorectal cancer

N. E. I. Langlois*, A. H. Ben Younes, J. Lamb*, O. Eremin and S. D. Heys, *Departments of Surgery and *Pathology, University of Aberdeen, Aberdeen, UK*

Recent interest in the control of tumour growth has focused on the relationship between cell proliferation and cell death (necrosis and apoptosis) The role of certain genes, p53 and Bcl-2, which play key role in controlling these processes, is becoming understood. The protein product of p53 has a key role in inducing apoptosis, whereas the Bcl-2 protein blocks apoptosis. These proteins can be detected in tumour cells by immunohistochemical techniques, but detection of the p53 protein has been demonstrated to imply loss of p53 function.

This study examined the relationships of apoptosis, mitosis and the expression of p53 and Bcl-2 protein products in colorectal cancer. In addition, their role as prognostic indicators was examined in conjunction with known prognostic indicators such as Dukes stage and extramural vascular invasion.

The tumours from 75 patients with colorectal cancer aged 45 years and under were staged using the Dukes staging system Apoptotic and mitotic counts and the presence of extramural vascular invasion were determined by light microscopy using standard criteria. The protein products of the p53 and Bcl-2 oncogenes were determined by means of a streptavidin–biotin technique. Tumours were regarded as positive for p53 or Bcl-2 if there was 10 per cent or greater staining of tumour nuclei.

A significant correlation was observed between apoptotic count and the mitotic index ($r = 0{\cdot}86$, $P = 0{\cdot}0003$). In addition, mean apoptotic count was increased in tumours not expressing the p53 protein product when compared with those in which it was detected (5·7 *versus* 4·3, $P = 0{\cdot}02$). There was, however, no relationship between p53 expression and mitotic count, or Bcl-2 expression and either apoptosis or mitosis.

Independent risk factors (Cox proportional hazard model) for overall survival were as follows: apoptotic count ($P < 0{\cdot}04$), Dukes stage ($P < 0{\cdot}0001$) and presence of extramural vascular invasion by tumour ($P < 0{\cdot}02$).

This study shows that apoptotic count is an independent prognostic indicator in patients with colorectal cancer. Furthermore, the increased expression of p53 protein (non-functional) suggests that p53 may have a key role in inducing apoptosis in these tumours. Therefore, the possibility that restoration of p53 function may improve survival has implications for gene therapy for cancer

Defunctioning colon causes alterations in the mucus defensive barrier in children

A. Aslam, R. D. Spicer, A. P. Corfield* and P. Durdy†, *Bristol Royal Hospital for Sick Children, *Department of Medicine Laboratories and †Department of Surgery, Bristol Royal Infirmary, Bristol, UK*

A number of patients having paediatric surgery undergo defunctioning colostomy for anorectal and colonic pathology. Because the mucus gel layer is the first line of colonic mucosal defence, changes in this layer in defunctioned colon (DC) were studied before the clinical appearance of diversion colitis. The aim was to demonstrate alterations in the mucus defensive barrier in DC in children.

An experimental model of mucosal culture was used with radioactive mucin glycoprotein precursors [^{35}S]sulphate and [^{3}H]glucosamine. After 24 h of culture the secretions were collected and the tissue homogenized and centrifuged to give the soluble fraction. The secreted fraction (SF) and cellular fraction (CF) were then filtered over columns of Sepharose 2B gel to obtain high-molecular-weight mucin glycoproteins. The mucin peak was collected and tested with wheatgerm agglutinin lectin (WGA), which is a good general-purpose reagent for mucin detection. The ratio of incorporation of the radioactive precursors and their turnover relative to tissue DNA content was determined to give a qualitative and quantitative assessment of radiolabelled mucin glycoproteins produced. Total mucin was analysed by reactivity with WGA and the turnover of total mucin was studied.

Six tissue samples were taken from defunctioned distal loop mucus fistulas at the time of colostomy closure and compared with six controls from functioning proximal colon. The ratio of incorporation of ^{35}S to ^{3}H in normal colon (NC) *versus* DC in the SF was 1·00 *versus* 0·54 and in the CF was 2·58 *versus* 0·39 (all values are median; *P* not significant). Radioisotope turnover in the SF for NC *versus* DC for ^{35}S was 1225 *versus* 279·9 ($P = 0{\cdot}03$) and for ^{3}H it was 2281·1 *versus* 824·6. Similarly in the CF the turnover for ^{35}S was 13892 *versus* 4406·7 and for ^{3}H it was 16011 *versus* 9953·4. Turnover (as measured by reactivity with WGA) in NC *versus* DC for the SF was 1·07 *versus* 1·04 and in the CF was 1·66 *versus* 1·29.

Clinically, none of these patients had colitis, so it is possible that the earliest changes of diversion colitis are mucus layer alterations. The results highlight a qualitative difference in mucin production in that the relative incorporation of ^{35}S is reduced in DC. Sulphation is known to increase mucin resistance to bacterial degradation. There is a global reduction in mucin turnover which is present in both the secreted and cellular fractions. This may indicate increased risk of bacterial colonization of mucosa, which could be a possible factor in the aetiology of diversion colitis.

Investigation of colonic pouch with and without seromyotomy following low anterior resection

A. F. Horgan, D. J. Waldron, C. B. O'Sullivan and W. O. Kirwan, *University Department of Surgery, Cork University Hospital, Cork, Ireland*

It has been suggested that the fashioning of a pouch neorectum from the residual colon can influence the functional outcome following low anterior resection (LAR). To study the physiological effects of a variety of neorectal types, four groups of six minipigs underwent LAR with restoration of continuity at the pelvic floor. Group 1 had a coloanal anastomosis (AR); group 2 also had three longitudinal seromyotomies (ARS); group 3 had a coloanal anastomosis with inclusion of a colonic pouch (ARP); group 4 had a colonic pouch with three longitudinal seromyotomies (ARPS). Physiological studies included basal sphincter pressure, neorectal capacity, neorectal compliance and whole-gut transit time.

Basal anal sphincter pressure was not significantly altered by any of the above procedures. Mean(s.d.) ARP (101·7(12) ml) and mean(s.d.) ARPS (113·3(15) ml) had significantly greater effect on neorectal capacity compared with AR (42·5(12) ml) and ARS (54·2(14) ml) ($P < 0{\cdot}001$). Compliance was also significantly greater following ARP (0·9(0·4)) and ARPS (0·8(0·4)) than AR (3·7(1)) or ARS (3·4(0·7)) ($P < 0{\cdot}001$). ARP led to a significantly greater delay of whole-gut transit time at 1 week after operation compared with AR and ARS ($P < 0{\cdot}05$). The effect was seen more markedly at 1 month ($P < 0{\cdot}001$). The addition of seromyotomy (ARS) led to a marginally significant slowing of transit at 1 month after operation ($P < 0{\cdot}05$). The addition of seromyotomies (ARPS) achieved significantly greater transit delay than with the pouch alone ($P < 0{\cdot}01$).

The fashioning of a colonic pouch has physiological benefits following LAR, causing a significant delay in transit time and improving capacity and compliance. The addition of seromyotomies to the pouch does not significantly alter the neorectal physiological parameters but has a beneficial effect by delaying transit time.

Does a colonic J pouch benefit all patients undergoing anterior resection for low rectal cancer?

M. Oya, J. Komatsu, Y. Takase, T. Nakamura and H. Ishikawa (introduced by M. R. B. Keighley), *Department of Surgery, Koshigaya Hospital, Dokkyo University School of Medicine, Saitama, Japan*

Anal function following anterior resection and coloanal anastomosis (CAA) for low rectal cancer is considered to be better with a colonic J pouch than without. However, it remains unclear whether all patients undergoing CAA benefit from a colonic J pouch. The aim of the present study was to explore the role of preoperative anorectal physiology tests in selecting patients likely to benefit from a colonic J pouch.

Twenty-three patients who underwent CAA for low rectal cancer were studied prospectively. A colonic J pouch was constructed in ten patients (J pouch group) and straight CAA was performed in 13 (straight group). Anorectal manometrical and sensory tests were carried out both before operation and 6 months afterwards. Anal function at 6 months after operation was clinically scored between 0 (best) and 6 (worst) from bowel frequency, severity and frequency of faecal incontinence, and severity of defaecatory urgency.

At 6 months after operation patients in the J pouch group had significantly better clinical anal function than those in the straight group (mean score 2·1 *versus* 3·2; $P = 0{\cdot}046$, Mann–Whitney U test). Maximum tolerated volume (MTV) of the neorectum was significantly greater in the J pouch group than in the straight group (median 140 *versus* 80 ml, $P = 0{\cdot}019$). Neither sphincter pressure nor anal mucosal sensitivity differed between the groups. Using multiple regression analysis, however, the postoperative function score of patients in the straight group was strongly correlated with preoperative MTV of the rectum (score 4·97 ± 0·011 × preoperative MTV (ml); $r = 0{\cdot}835$, $P = 0{\cdot}0004$). When patients in the J pouch group were assessed, preoperative MTV had a larger influence than the type of reconstruction: postoperative function score 4·57 ± 0·008 × preoperative MTV (ml) ± 1·05 × reconstruction type (J pouch, 1; straight, 0). Overall the multiple correlation was 0·712, whereas the standard coefficient for MTV and reconstruction type was −0·532 and −0·379 respectively.

These results suggest that patients with a small preoperative MTV may derive more functional benefit from a colonic J pouch than those with a large preoperative MTV.

Outcome and predictors of success of biofeedback for constipation

R. Gilliland, S. Heymen, D. F. Altomare, U. C. Park, D. Vickers and S. D. Wexner (introduced by K. R. Gardiner), *Cleveland Clinic Florida, Fort Lauderdale, Florida, USA*

Published studies of biofeedback for constipation have generally included small numbers of patients with short follow-up periods. This study was undertaken to determine outcome and to identify predictors of success for biofeedback in the treatment of these patients.

Patients who had at least one biofeedback session between March 1989 and August 1995 were evaluated whether or not they had completed a treatment course. All sessions were 1-h outpatient encounters with a trained biofeedback therapist. Parameters assessed included use of cathartics, number of spontaneous bowel movements (SBMs) per week, presence of rectal pain, number of biofeedback sessions and results of physiological testing (electromyography, cinedefaecography, colonic transit study). Positive test results were those in which pelvic outlet obstruction was demonstrated.

Some 191 patients (59 male, 132 female) of median age 71 (range 11–96) years, including 36 (18·8 per cent) with concomitant rectal pain, were treated. The median number SBMs per week before treatment was 0. Patients who had only one session ($n = 13$) were excluded from further analysis. At the end of the 6-year period, outcome in the remaining 178 patients was categorized as good (three or more SBMs per week with discontinuation of cathartics) in 35·4 per cent, fair (fewer than three SBMs per week with continued use of cathartics) in 13·5 per cent and poor (no improvement) in 51·1 per cent. Treatment outcome was not significantly related to age, sex, duration of symptoms or concomitant rectal pain. Only 18·3 per cent of patients who had two to four biofeedback sessions had a good outcome, compared with 44·1 per cent who attended for five or more ($P < 0{\cdot}001$, Fisher's exact test). A good outcome was achieved in 24·8 per cent of patients who self-discharged compared with 63·3 per cent who completed treatment ($P < 0{\cdot}0001$). In 146 patients who had at least two physiological tests, the outcome depended on the number of positive tests: 28·1 per cent if two or three tests were positive compared with 45·1 per cent if no or one test was positive ($P < 0{\cdot}05$).

This large study indicates that the success rate of biofeedback for patients with constipation is lower than that reported previously. However, success rates improve with patient compliance and after five or more sessions. Biofeedback is less likely to be successful in patients with two or more physiological tests positive for pelvic outlet obstruction.

Preoperative assessment of the probability of lymph node metastasis from rectal carcinoma

U. A. Khimaira, K. W. Robertson, T. G. Cooke, I. G. Finlay and D. Hemingway, *University Department of Surgery, Glasgow Royal Infirmary, Glasgow, UK*

Curative local resection of rectal carcinoma requires that there be no lymph node metastasis (LNM). A scoring system has been developed that determines the probability of LNM. Some 50 patients with rectal carcinoma, of whom 16 (32 per cent) had LNM, were studied. Depth of tumour invasion was determined from histology Invasion limited to submucosa, into muscularis propria and through the bowel wall scored 0, 1·5 and 3 respectively. Tumours were categorized as well, moderately and poorly differentiated (score 0, 1 and 2 respectively). Ploidy was determined using flow cytometry; diploid and aneuploid scored 0 and 1 respectively. Depth of invasion was found to be significantly associated with LNM ($P = 0{\cdot}031$, χ^2 test). Ploidy showed no association, but there was a trend to poorer differentiation in tumours with LMN ($P = 0{\cdot}053$); combining the histological factors provided a statistically significant index ($P = 0{\cdot}043$). Using this scoring system, a summed score for all three factors was highly significantly associated with LNM ($P < 0{\cdot}001$, Mann–Whitney *U* test).

Score	*n*	LNM (%)
$x<3$	12 (24)	0
$3 \le x \le 4$	20 (40)	25
$4 < x \le 5$	16 (32)	56
$x > 5$	2 (4)	100

Values in parentheses are percentages. x is the summed score. $P = 0{\cdot}0008$ (Mann–Whitney *U* test)

Transanal ultrasonography can provide a measure of depth of invasion, but is operator dependent and requires specialist equipment. Grade and ploidy can be determined from routine biopsy specimens and can be performed at a distant centre; together these indices may be as useful as depth of invasion at indicating the risk of LNM. The table clearly indicates that ideally all three should be measured.

A new look at the anal transitional zone – shorter than previously described and can be safely retained

M. W. Thompson-Fawcett, B. F. Warren and N. J. McC. Mortensen, *Departments of Colorectal Surgery and Cellular Pathology, John Radcliffe Hospital, Oxford, UK*

The anal transitional zone (ATZ) has been defined by Fenger as the zone interposed between uninterrupted colorectal type mucosa above and uninterrupted squamous epithelium below. He described mapping the ATZ and quantifying it by whole-specimen staining of the anus with Alcian blue and demonstrated a mean ATZ span of 8·9 mm.

This paper describes a new technique for mapping the ATZ by computer image processing of the microscopy from multiple longitudinal sections through the anus at 3-mm intervals. Sixteen anuses have been studied by this and the Alcian blue technique. Computer maps and photographs of specimens stained with Alcian blue were assessed by computer image analysis, measuring the areas and positions of the epithelial components, ATZ, dentate line and the lower border of the internal sphincter.

	Alcian blue technique	Computer map
Transitional (area per cm of anus)	0·65(0·13)	0·24(0·06)
Transitional zone span (cm)	0·66(0·14)	0·33(0·07)
Dentate line height (cm)	1·05(0·07)	0·95(0·08)
Upper border TZ (cm)	1·50(0·14)	1·45(0·09)
Lower border TZ (cm)	0·75(0·09)	1·08(0·07)

Values are median(s.e)

Columnar islands in the ATZ were infrequent (median number 0·5 (range 0–16); median area per ATZ 0·01 cm^2). The Alcian blue technique overestimated the amount of transitional epithelium in comparison with the histology ($P < 0{\cdot}01$, Wilcoxon signed rank test) by significant staining of the nuclei of non-keratinized simple squamous cells.

On the basis of this work there seems little concern about retaining the ATZ in restorative proctocolectomy and attention should be focused on the columnar cuff of mucosa in the anal canal between the pouch–anal anastomosis and the upper border of the ATZ.

Outcome of restorative proctocolectomy if the diagnosis is Crohn's disease

H. T. Tan, M. R. B. Keighley, S. Korsgen and D. Morton, *University Department of Surgery, Queen Elizabeth Hospital, Birmingham, UK*

Twenty-eight (16·8 per cent) of 167 patients who had restorative proctocolectomy for presumed ulcerative colitis are now thought to have Crohn's disease. One-stage proctocolectomy was used in 55 patients, of whom seven (13 per cent) were identified as having Crohn's disease from: colectomy specimen (four), later complications such as pouch–anal stricture (one) and pouch excision (two). Staged resection was performed in 112 patients, of whom 21 (18·8 per cent) were identified as having Crohn's disease from. colectomy specimen (four), excised rectum (three), later complications such as pouch–anal stricture (three), ileal stricture (two), pouch-related fistula (eight) and pouch excision (one).

Seventeen of 28 patients diagnosed as having Crohn's disease had an intact functioning ileoanal anastomosis. Two patients were permanently defunctioned because of patient preference (one) and a persistent pouch–vaginal fistula (one) Nine patients had pouch excision as a result of pouch-related fistula (five) and poor pouch function (four).

Ten of the 11 patients with Crohn's disease identified in the resection specimen had an intact functioning pouch, compared with only nine of 17 diagnosed as having Crohn's disease from later complications. Thus, it may not necessarily be a mistake to advise ileopouch–anal anastomosis in a comprehensively counselled patient in whom the possibility of Crohn's disease is raised from the histology of the resected specimen.

Pouch salvage: long-term outcome

M. R. B. Keighley, S. Korsgen and O. A. Ogunbiyi, *University Department of Surgery, Queen Elizabeth Hospital, Birmingham, UK*

An analysis was made of the outcome of 40 pouch salvage procedures in 209 patients having restorative proctocolectomy (RP) between 1984 and 1994 for ulcerative colitis (UC; $n = 145$), Crohn's disease (CD; $n = 10$), intermediate colitis (IC; $n = 6$), familial adenomatous polyposis (FAP; $n = 28$), megacolon (M; $n = 12$) and chronic constipation (C; $n = 8$). There were 11 operations for pouch–perineal ($n = 3$, UC) or pouch–vaginal ($n = 8$; 6UC, 1CD, 1C) fistulas, all arising from the dentate line. Salvage was uniformly successful for the four vaginal fistulas where there was no underlying CD or IC, using either a seton (three patients) or advancement flap (one). The results of attempts to clear pouch–perineal fistula were uniformly unsuccessful (all had had anorectal sepsis before pouch construction). There were eight operations for pouch–cutaneous fistula (7UC, 1M) but three involving the ileoanal anastomosis failed. Three patients had pouch construction after conservative proctocolectomy (3UC); all were successful and all suffer from soiling. Four patients have had attempted salvage for chronic sepsis at the ileoanal anastomosis by reanastomosis or advancement flap (3UC, 1IC); only two were successful. Three patients have had strictures in or just above the pouch treated by strictureplasty (1UC, 1CD, 1M); two were successful. Two patients with a long efferent limb (1CD, 1UC) have been treated by excision and anastomosis; both were successful. Two with pouch prolapse were successfully treated by pouchpexy (1UC, 1C). Three patients who lost the original pouch as a result of ischaemia had a new one constructed (3UC); all have had a poor result and now live with an ileostomy. Four patients had secondary surgery for incontinence (pelvic floor repair, three; graciloplasty, 1; 1UC, 2M, 1C); only two were successful.

Twenty-two of 40 patients having pouch salvage had a successful procedure. Poor results were associated with CD, chronic sepsis and new pouch formation.

Pouch survival

S. Korsgen and M. R. B. Keighley, *University Department of Surgery, Queen Elizabeth Hospital, Birmingham, UK*

A review was carried out of 177 patients with ileoanal pouches constructed over 10 years and followed for at least 2 years (135 ulcerative colitis (UC), ten with a postoperative diagnosis of Crohn's disease (CD), six with indeterminate colitis (ID) and 26 for familial adenomatous polyposis (FAP)). Some 23 pouches have been excised to date; eight remain defunctioned.

The reasons for excision were: ischaemia (six patients), pelvic sepsis (five), severe stenosis (three), underlying Crohn's disease (three), poor function (five) and fistula (one). The reasons for defunction were: Crohn's disease (one), pelvic sepsis (five) and ileoanal stenosis (two).

The projected overall pouch survival rate (life-table analysis) at 5 years was 81 per cent (confidence interval 74–87 per cent)

Four of the six pouches in patients with ID were excised, and four of ten pouches in those with CD. Only two pouches for FAP failed.

There was a significant association between pouch failure and pelvic sepsis ($P < 0·0001$ Fisher's exact test) and fistula ($P < 0·02$), but only a trend with pouchitis ($P = 0·124$) and ileoanal stenosis ($P = 0·068$).

Patients should be warned that failure after pouch construction may be related to undisclosed CD or ID and chronic pelvic sepsis.

Reduced long-term survival following major haemorrhage from peptic ulcer

A. K. Kubba, C. Choudari, C. Rajgopal and K. R. Palmer (introduced by R. G. Wilson), *Gastrointestinal Unit, Western General Hospital, Edinburgh, UK*

The late outcome of patients who present with major haemorrhage from peptic ulcer is unclear. Some 105 patients treated endoscopically for severe peptic ulcer haemorrhage were followed for a median of 36 (range 30–76) months and outcome was compared with that in age- and sex-matched controls, obtained from the Scotland Mortality Report of 1993.

All patients had presented with major endoscopic stigmas of haemorrhage; age ranged between 30 and 96 (median 68) years. Some 46 per cent of patients had significant co-morbid disease.

Kaplan–Meier plots showed reduced survival in patients with an ulcer ($P < 0·001$).

Twenty-nine patients died during the follow-up period; death was restricted largely to patients who had co-morbid disease. Seven of the remaining 76 patients had further peptic ulcer bleeding; two of these were taking maintenance acid-reducing therapy and only one had significant dyspepsia before re-bleeding.

Data from a validated dyspepsia questionnaire showed that 83 per cent of surviving patients had little or no dyspepsia, while four had severe dyspepsia despite appropriate ulcer medication.

The late prognosis of patients who present with major ulcer haemorrhage is poor, but most deaths are a consequence of co-morbid disease and not recurrent ulcer bleeding. Most patients have little dyspepsia and many who rebleed are free from dyspepsia.

Incidence of rejection in combined liver–total bowel transplantation *versus* total bowel transplantation alone: a prospective study in a porcine model

N. Hakim, J. Pirenne*, V. Papalois and R. W. G. Gruessner (introduced by A. Mansfield), *Transplant Unit, St Mary's Hospital, London, UK and *Department of Surgery, University of Minnesota, Minneapolis, Minnesota, USA*

It has been suggested from small animal studies that the liver graft may protect the simultaneously transplanted bowel from rejection.

In a preclinical pig model a study was made of the addition of a liver graft to the transplanted bowel *versus* a solitary bowel transplant with regard to survival, rejection and graft *versus* host disease (GVHD).

Yorkshire Landrace pigs underwent either combined liver–total bowel transplantation (LTBTx; group 1, $n = 9$) or solitary total bowel transplantation (TBTx; group 2, $n = 5$). In group 1 animals, liver, small and large bowel were transplanted *en bloc*. Pigs in group 2 underwent portally drained TBTx In both groups intravenous FK506 ($0·2\,\mathrm{mg\,kg^{-1}day^{-1}}$) and prednisolone ($2\,\mathrm{mg\,kg^{-1}day^{-1}}$) were given for induction and maintenance therapy. Biopsies were obtained daily from the ileostomy to study the incidence of graft rejection.

Pig survival rate on post-transplant days 7, 10, 14, 21 and 28 was 100, 78, 22, 11 and 0 per cent respectively in group 1 (deaths from infection and surgical complications) *versus* 100, 100, 100, 100 and 60 per cent in group 2 (deaths from infection and GVHD). There were no rejection-related deaths. Daily biopsies showed that rejection grades were significantly better in group 2 animals on individual days; the difference was not significant over time ($P = 0·2$). In both groups, vascular rejection was encountered in less than 10 per cent of daily biopsies.

Pigs with LTBTx had a higher infection and surgical complication rate than those with TBTx. FK506 was effective in preventing graft loss from rejection in both groups. LTBTx has no immunological advantage over TBTx, as the incidence of rejection is not different between the two groups.

Internal biliary drainage reverses intestinal permeability changes in jaundiced patients

R. W. Parks, W. D. B. Clements, M. Smye*, B. J. Rowlands and T. Diamond, *Departments of Surgery and *Clinical Biochemistry, The Queen's University of Belfast, Belfast, UK*

Impaired intestinal mucosal barrier function has been implicative in the pathophysiology of complications seen with obstructive jaundice. This study investigated intestinal permeability in jaundiced patients and examined the effect of internal biliary drainage.

Intestinal permeability was assessed using the lactulose–mannitol absorption test. Forty-five jaundiced patients and ten non-jaundiced controls were studied before operation (day −1) and on days 1, 7 and 28 following surgical, endoscopic or percutaneous internal biliary drainage. In addition 11 healthy volunteers were assessed.

The mean(s.e.m.) lactulose : mannitol ratio for healthy volunteers was 0·020 (0·003). Results for the patients are expressed as mean(s.e.m.) at each timepoint.

	Day −1	Day 1	Day 7	Day 28
Jaundiced patients ($n = 45$)	0·046(0·008)*	0·054(0·008)	0·040(0·009)	0·021(0·004)†
Non-jaundiced patients ($n = 10$)	0·016(0·002)	0·033(0·007)	0·026(0·007)	0·020(0·003)

*$P < 0·0001$ *versus* control patients (Mann–Whitney U test); †$P < 0·05$ *versus* day −1 (Wilcoxon signed rank test)

Obstructive jaundice results in increased intestinal permeability, which is reversed by internal biliary drainage. Improving intestinal mucosal barrier function may be an effective therapeutic strategy in preventing septic and other complications in obstructive jaundice.

Photodynamic therapy for Barrett's oesophagus: a dosimetric pilot study

R. Ackroyd, D. J. H. Roberts*, D. I. Vernon*, N. J. Brown and M. W. R. Reed, *University Department of Surgery, Royal Hallamshire Hospital, Sheffield and *Department of Biochemistry, University of Leeds, Leeds, UK*

The use of aminolaevulinic acid (ALA)-induced photodynamic therapy (PDT) may provide effective eradication of malignant and dysplastic tissues. ALA induces cellular production of the photosensitizer protoporphyrin IX (PpIX), which is then activated by light to cause cell damage. The optimal drug dosage and time to light delivery need to be established.

Twenty-eight patients with dysplastic Barrett's oesophagus were randomized to receive oral ALA (30 or 50 mg kg^{-1}) or placebo. Endoscopic biopsies were taken at 2, 4 or 6 h and analysed for PpIX content by spectrofluorimetry and high-performance liquid chromatography (HPLC). Fluorescence microscopy was used to identify the site of PpIX accumulation.

At 50 mg kg^{-1} oesophageal discomfort, hair loss and transient derangement of liver function test results were observed. With 30 mg kg^{-1} an adequate increase in PpIX levels was seen (see *Table*), with few or no side-effects.

	Pp IX (ng per mg tissue)		
Oesophagus	2 h	4 h	6 h
Normal	2·7(0·3)	3·2(0·5)	2·8(0·2)
Barrett's	2·5(0·6)	2·9(0·3)	1·9(0·1)*

Values are mean(s.e.m.) ($n = 4$). *$P < 0·05$ *versus* normal (analysis of variance/Mann–Whitney U test)

In all patients receiving ALA, PpIX levels were significantly higher than in those having placebo (0·9(0·05) ng mg^{-1}, $P < 0·05$). HPLC confirmed more than 90 per cent of PpIX content and fluorescence microscopy revealed maximal PpIX accumulation in the mucosa.

Therefore ALA 30 mg kg^{-1} orally followed 4 h later by light administration provides optimal treatment conditions for PDT in Barrett's oesophagus.

Intestinal metaplasia at the gastro-oesophageal junction: a new risk factor for adenocarcinoma?

C. K. MacKay, I. Hadia, R. Carter, J. Going*, J. N. Baxter and R. C. Stuart, *University Departments of Surgery and *Pathology, Glasgow Royal Infirmary, Glasgow, UK*

The incidence of oesophageal adenocarcinoma is increasing and Barrett's oesophagus is the main risk factor. The risk is greatest when intestinal metaplasia is present. Intestinal metaplasia at the squamocolumnar junction without endoscopically apparent Barrett's oesophagus has been reported recently and is termed short-segment Barrett's oesophagus. The aim of this study is to determine the prevalence of short-segment Barrett's oesophagus in patients attending for diagnostic endoscopy and to investigate the role of *Helicobacter pylori* in its pathogenesis.

Some 86 patients with normal endoscopic findings were studied. Biopsies were taken from stomach, squamocolumnar junction, squamous oesophagus, and an antral CLO test (for *H. pylori*) was performed.

Intestinal metaplasia at the squamocolumnar junction was found in 24 patients (M : F ratio 1·67, median age 55·5 years); there was no intestinal metaplasia in 62 (M : F ratio 0·68; median age 49·5 years). In patients with short-segment Barrett's oesophagus the distance between the oesophagogastric and squamocolumnar junctions was 0 cm in 13, 1 cm in nine and 2 cm in two patients. One patient had low-grade dysplasia. Only four of the short-segment group had intestinal metaplasia elsewhere in the stomach.

	Normal ($n = 62$)	Short segment ($n = 24$)	χ^2	P
Antral *H. pylori* positive	27 (44)	15 (62)	2·49	0·115
Oesophagogastric junction				
H pylori positive	23 (37)	13 (54)	2·07	0·15
Histological gastritis	46 (74)	19 (79)	0·23	0·63

Values in parentheses are percentages

Intestinal metaplasia is present at the squamocolumnar junction in 28 per cent of patients without endoscopically apparent Barrett's oesophagus. This may represent a previously unrecognized risk factor for adenocarcinoma of the oesophagogastric junction.

Tumour suppressor gene deletions in oesophageal adenocarcinoma

R. Morgan, A. Perry, P. Newcomb, M. Bailey, R. Hardwick and D. Alderson, *Department of Surgery, Bristol Royal Infirmary, Bristol, UK*

Loss of cell cycle control is believed to be an important step in the development of human tumours. A number of tumour suppressor genes are involved in control of the cell cycle, including p16, p53 and the retinoblastoma (Rb) gene. The aim of this study was to look for deletions of these tumour suppressor genes in oesophageal adenocarcinoma.

Paired (tumour and normal) frozen tissue samples from 12 patients were analysed by polymerase chain reaction (PCR) to seek loss of heterozygosity (LOH) at five microsatellite marker sites (IFNA and D9s171 for p16, D13s118 and D13s133 for Rb, and a marker at the p53 gene locus). Aneuploid cell populations from the tumours were sorted by flow cytometry before PCR, to eliminate contamination by stromal cells.

Of the 12 tumours, 11 had LOH at one or more loci. Forty-seven loci were informative, with LOH at 27. LOH at the p53 locus occurred in nine of 12 tumours, at one or both p16 loci in seven of 11 tumours, and at one or both Rb loci in eight of 12 tumours. Five tumours had LOH at two tumour suppressor gene loci (p53 and p16 in one; p53 and Rb in two; p16 and Rb in two), and a further four tumours had LOH at loci for all three genes.

These results indicate that loss of cell cycle control, as a result of deletions in tumour suppressor genes, may be important in the development of oesophageal adenocarcinoma. In particular, these events may be involved in the generation of aneuploid cell populations.

Effect of bupivacaine on postoperative pain and pulmonary function after laparoscopic cholecystectomy

D. H. Wallace, M. G. Serpell and P. J. O'Dwyer, *University Department of Surgery, Western Infirmary, Glasgow, UK*

Previous studies have suggested that intraperitoneal local anaesthesia may have a significant effect on postoperative pain after laparoscopy. The aims of this study were to evaluate the effects of intraperitoneal bupivacaine 0·25 per cent with adrenaline, and port-site infiltration with bupivacaine, on postoperative pain and pulmonary function following laparoscopic cholecystectomy. Forty patients were randomized in a double-blind placebo (saline)-controlled trial. Results for intraperitoneal bupivacaine are shown in the *Table*.

	Bupivacaine	Saline	P
Pain*			
6 h	64 (37–76)	38 (15–64)	0·005
24 h	49 (42–75)	39 (23–66)	0·05
PEFR†			
6 h	64 (48–75)	73 (61–87)	0·89
24 h	59 (46–83)	73 (47–92)	0·72
Hospital stay (days)	2 (1–2)	1 (1–2)	0·51

Values are median (interquartile range), expressed as a percentage of *biliary symptom score and †preoperative level. PEFR, peak expiratory flow rate

Patients receiving intraperitoneal bupivacaine had significantly more postoperative nausea and vomiting ($P < 0·04$). There were no differences in postoperative analgesia requirements between groups. Port-site bupivacaine had no effect on postoperative pain and pulmonary function. These results show that intraperitoneal local anaesthesia may have a deleterious effect on postoperative recovery following laparoscopic cholecystectomy.

Value of positron emission tomography using fluorodeoxyglucose for imaging pancreatic lesions (benign and malignant)

A. H. Ben Younes, C. Campbell*, F. W. Smith*, N. T. S. Evans†, S. D. Heys, Z. H. Krukowski, P. Sharp† and O. Eremin, *Departments of Surgery, *Nuclear Medicine, and †Biomedical Physics and Bioengineering, University of Aberdeen Medical School, Aberdeen, UK*

A range of conventional imaging techniques has been used to examine the topographical anatomy of the pancreas. In contrast, positron emission tomography (PET) provides an *in vivo* insight into tissue and tumour function. Positron emitter-labelled metabolic substrates are introduced into the circulation; following tissue uptake, they decay to release two photons that register on computerized detectors.

Fluorodeoxyglucose (FDG) is a positron emitter-labelled glucose analogue that demonstrates preferential uptake by human tumours, when compared with normal tissue. This increased uptake is secondary to increased glycolysis and enhanced membrane transport of glucose.

The aims of this study were to evaluate the role of FDG PET in imaging pancreatic carcinoma and to assess its value in differentiation between benign and malignant pancreatic tumours.

Some 23 patients underwent FDG PET to assess the pancreas. Following intravenous injection of FDG, transaxial PET images were obtained using the ECAT II scanner. In all, 19 patients were diagnosed as having pancreatic carcinoma, 18 of which demonstrated selective FDG uptake at the site of the tumour. Only one patient with pancreatic carcinoma was shown to have no increased FDG uptake at the tumour site. Four patients in this study who had inflammatory pancreatic masses did not demonstrate any increase in FDG uptake in the region of the pancreas.

This study has shown FDG PET scanning to be a sensitive test for diagnosing pancreatic cancer and, although it involved only a small number of patients, the results suggest that this is also a specific test, allowing differentiation between inflammatory and neoplastic tumours.

Experimental studies on injection therapy for ulcer haemorrhage in rabbits

A. K. Kubba, A. Lessells and K. R. Palmer (introduced by R. G. Wilson), *Gastrointestinal Unit, Western General Hospital, Edinburgh, UK*

Endoscopic injection therapy is a well established method of controlling peptic ulcer haemorrhage but the optimum solution and the mechanism involved in inducing haemostasis are unknown. The efficacy and tissue effects of various therapeutic agents used in the control of gastric mucosal haemorrhage were assessed in ten rabbits. Thirty-eight bleeding mucosal ulcers created at gastrotomy (blood loss greater than 1·5 ml min^{-1}) were studied. Adrenaline (1:100 000), thrombin, fibrin (thrombin plus fibrinogen), 5 per cent ethanolamine and 50 per cent dextrose were injected and a fibrin suspension was sprayed into bleeding ulcers.

Sclerosants were found to be least effective in the control of bleeding and were associated with significant tissue necrosis. Although all the other solutions significantly decreased blood loss within 30 min of injection therapy (median blood loss 0·25 ml min^{-1}), only an injection mixture of adrenaline plus thrombin and sprayed fibrin achieved complete haemostasis within 2 min of treatment and with no recurrence of bleeding. Neither modality caused significant tissue damage.

Histological examination showed that no injected solution caused arterial thrombosis when injected next to a major ear artery.

It is concluded that a combination of dilute adrenaline plus human thrombin may represent optimal haemostatic therapy for peptic ulcer haemorrhage.

Endothelial cell markers and the extent of atherosclerosis

A. D. Blann, M. Seigneur*, M. Boisseau* and C. N. McCollum, *Department of Surgery, University Hospital of South Manchester, Manchester, UK and *Department of Haematology, University of Bordeaux, France*

Damage to the endothelium may predispose to the development of atherosclerosis. To investigate how markers of endothelial integrity relate to the severity and extent of disease, levels of three specific markers of endothelial function, von Willebrand factor (vWF), soluble thrombomodulin (sTM) and soluble E-selectin (sE-sel), were determined by enzyme-linked immunosorbent assay in the plasma of 200 patients with symptomatic atherosclerosis at one or more sites (carotid and/or iliac–femoral and in 213 age- and sex-matched asymptomatic controls.

	Control ($n = 213$)	One site ($n = 142$)	Two or more sites ($n = 58$)	P for trend*
sTM (ng ml^{-1})	44(14)	61(22)†	73(28)‡	< 0·001
sE-sel (ng ml^{-1})	54(19)	55(21)	60(23)	0·21
vWF (units dl^{-1})	100(36)	134(38)†	137(40)	< 0·001

Values are mean(s.d.) *One-way analysis of variance. †$P < 0·05$ *versus* control, ‡$P < 0·05$ *versus* patient groups (Tukey's test)

There was no change in level of sE-sel in patients but vWF was raised regardless of the extent of disease. However, sTM was increased in proportion to the extent of disease. sTM may be a novel marker for the extent of endothelial cell damage in atherosclerosis.

Is niroscopy a reliable tool for assessing cerebral metabolism during carotid endarterectomy?

A. J. McCleary, P. Braithwaite, A. Bodenham and M. J. Gough, *Vascular Surgical Unit, The General Infirmary at Leeds, Leeds, UK*

Near infrared spectroscopy (NIRS; niroscopy) has been advocated as a reliable technique for assessing cerebral oxygenation during carotid endarterectomy (CE), although doubts remain regarding its validity in view of the potential for changes in extracerebral perfusion or the relative proportions of intracerebral venous–arterial blood volumes required to influence the results obtained.

CE, with sequential occlusion of the external (ECA) and common (CCA) carotid arteries, provides a model ischaemia that can be used to validate the technique. Some 50 patients undergoing CE were monitored with NIRS and continuous jugular venous oximetry. While changes in the jugular venous saturation ($S_{\mathrm{JvO_2}}$) should reflect alterations in cerebral oxygenation, it should not be affected by changes in extracerebral oxygenation (clamping ECA) or by variations in arterial–venous blood volumes. During CE, changes in the cerebral concentration of oxyhaemoglobin and cytochrome oxidase (NIRS) and $S_{\mathrm{JvO_2}}$ were recorded at 1-s intervals. Oxyhaemoglobin concentration fell in 74 per cent of patients on ECA occlusion, with a further fall (94 per cent) when the CCA was clamped. $\mathrm{Caa_3}$ levels altered similarly. $S_{\mathrm{JvO_2}}$ also fell in 92 per cent of patients when the CCA was clamped When these changes were plotted against those for oxyhaemoglobin for each patient, the mean correlation coefficient was 0·8 (range 0 55–0·95) ($P<0\,001$).

These results provide strong evidence that the changes measured by niroscopy accurately reflect alterations in cerebral metabolism. This non-invasive technique may thus have an important role in monitoring cerebral metabolism both during CE and in other circumstances where cerebral oxygenation may be compromised.

Should heparin be reversed after carotid endarterectomy?

S. J. Fearn, A. D. Parry, A. J. Picton, A. J. Mortimer and C. N. McCollum, *University Hospital of South Manchester, Manchester, UK*

Wound haematoma is the most frequent complication of carotid endarterectomy and may occasionally cause respiratory distress. Protamine is widely used to reverse heparin but has never been tested by clinical trial A randomized double-blind trial of heparin reversal with protamine was carried out on 64 patients taking aspirin who were given heparin 70 units kg^{-1} before cross-clamping. Serial activated clotting times were used to plot a dose–response curve to calculate protamine dosage. Postoperative wound drainage and incidence of haematoma were recorded. Neck swelling was measured using ultrasonography to record the depth of the carotid bifurcation.

	Non-reversed ($n=33$)	Reversed ($n=31$)
Activated clotting time (s)		
Preheparin	100 (93–109)	106 (96–112)
Postheparin	252 (220–300)	226 (201–252)
Arteriotomy closure	182 (171–204)	95 (89–102)*
Wound drain (ml)	77 (50–150)	25 (17–35)*
Neck swelling (mm)	70 (48–78)	72 (50–96)

Values are median (interquartile range). *$P<0·01$ *versus* non-reversed (Mann–Whitney U test)

Reversing heparin significantly reduced wound drainage and two non-reversed patients developed neck haematomas requiring re-exploration. However, three reversed patients developed internal carotid thrombosis within 12 h, two of whom died despite urgent thrombectomy.

Although protamine reversal of heparin following carotid surgery may preclude wound drains, it may be associated with internal carotid artery thrombosis

Correlating popliteal artery flow and skin blood flux changes in health and peripheral vascular disease

K. Delis, A. N. Nicolaides, N. Labropoulos and G. Stansby, *Academic and Regional Vascular Unit, St Mary's Hospital, Imperial College, London, UK*

Assessment of the microcirculation may provide easily accessible information regarding blood flow in the lower limb in health and disease. However, flow responses in the lower-limb arteries and skin vessels have never been investigated comparatively in relation to changes in posture. This study aimed to evaluate the effect of postural alteration on popliteal artery blood flow (PABF) and skin blood flux (SBF) in the foot and to determine the relationships between flow changes in these two systems.

Some 50 limbs of normal subjects and 50 limbs of stable claudicants were examined using duplex ultrasonography (HP Sonos 2500) and laser Doppler fluxmetry (Laserflo BPM 403), and estimations of PABF and SBF (dorsum of the foot) were obtained in the reclining and sitting positions. The percentage change in PABF on postural alteration (PABF (per cent) = horizontal flow–sitting flow/horizontal flow × 100) and the venoarteriolar reflex (VAR) were compared per limb per study group using linear regression analysis (LRA).

LRA for percentage PABF against VAR gave a correlation coefficient of 0·60 in the normal group ($t=5·1$, $P<0·001$) and 0·84 in the disease group ($t=10·5$, $P<0·001$). Mean(s.d.) PABF was 50(12) per cent in controls and 44(16) per cent in claudicants ($P=0·042$) (95 per cent confidence interval 0·25–11·63 per cent). Mean(s.d.) VAR was 57(12·3) per cent in controls and 50·3(17) per cent in claudicants ($P=0·104$).

Postural alteration produces consistently similar changes in PABF and SBF in both health and peripheral vascular disease. Presumably the vasoconstrictor response in the microcirculation is responsible for the similar pattern of change seen in the macrocirculation. Stable claudicants, however, have a significantly lower vasoactive response than normal subjects, possibly reflecting a derangement of the venoarteriolar response.

Adaptation of saphenous vein endothelium to arterial flow

J. Golledge, R. J. Turner, S. L. Harley, D. Springall and J. T. Powell, *Department of Surgery, Charing Cross and Westminster Medical School, London, UK*

Saphenous vein is the conduit most commonly used for revascularization. Successful adaptation to the high-pressure pulsatile flow of the arterial circulation could be critical to the outcome of vein bypass. This study investigated the early changes in saphenous vein endothelium in response to arterial flow.

Segments of human saphenous vein were placed in a circuit for up to 90 min and exposed to pulsatile flow at 100 mmHg (arterial flow) and non-pulsatile flow at 20 mmHg (venous flow). Endothelium-dependent relaxation of vein rings in response to A23187 (nitric oxide pathway) and fibrinogen (intercellular adhesion molecule (ICAM) 1-dependent pathway) were assessed. Nitric oxide synthase (eNOS), ICAM-1, vascular cell adhesion molecule (VCAM) 1 and cell determinant (CD) 31 expression were estimated by immunohistochemistry and Western blotting of harvested endothelial cells. Staining was quantitated by computer-assisted analysis.

	Flow circuit			
			Arterial	
	Basal 0 min ($n=22$)	Venous 90 min ($n=6$)	45 min ($n=8$)	90 min ($n=8$)
Relaxation (%)*				
A23187	53·1(3·0)	54·4(4·0)	67·5(3·0)‡	68·6(3·0)‡
Fibrinogen	55·0(4·9)	55·0(4·9)	90·0(5·4)§	97·0(2·1)§
Immunostaining area†				
eNOS	51·4(6·0)	45·3(6·0)	59·8(6·0)	70·1(5·0)§
ICAM-1	23·7(3·0)	34·5(2·8)	42·8(3·8)§	44·6(2·5)§
VCAM-1	16·6(3·4)	25·1(3·0)	5·0(1·5)§	1·8(0·5)§

Values are *maximum(s.e.) and †percentage(s.e.) of CD31 staining. ‡$P<0·05$, §$P<0·01$

Western blotting confirmed a 4–5-fold increase in eNOS ($n=6$) and a 3–4-fold increase in ICAM-1 ($n=6$) expression after 90 min of arterial flow.

Exposure of saphenous vein to arterial flow results in early changes in products that control the adhesiveness of the endothelium. The prompt upregulation of ICAM-1 could encourage leucocyte and fibrinogen binding before the later increase in eNOS acts to minimize these adverse effects.

Community leg ulcer clinics: a comparative study in two health districts

D. A. Ellison, L. Groarke, L. Freak, J. Walsh, C. Lane, A. M. Kinsella and C. N. McCollum, *Department of Surgery, University Hospital of South Manchester, Manchester, UK*

This prospective study measured the cost and effectiveness of leg ulcer care across two health authorities of populations 290 000 and 250 000. The standard approach to leg ulcer care in both authorities reflected the service throughout the UK, being expensive and ineffective. Detailed prospective data over a 3-month period were collected in the two health authorities both before and 1 year after the introduction of five community leg ulcer clinics into one authority; the other acted as a control.

The introduction of community clinics improved leg ulcer healing over 3 months from 66 (26 per cent) of 252 initially to 99 (42 per cent) of 233 1 year later ($P<0{\cdot}001$, χ^2 test). In the control district only 43 (20 per cent) of 213 ulcers had healed over the same period by the end of the project. Total staff time in leg ulcer care over 3 months was reduced from 2610 to 1813 h ($P<0{\cdot}001$) in the test district, resulting in a reduction in annual staff costs of £77 097 (31 per cent), from £252 439 to £175 342 over the first year of the project. In the control health authority, staff time increased from 3018 to 3047 h with annual staff costs rising by 1 per cent to £294 675. Improved healing in community clinics was achieved, while the total annual leg ulcer care costs were reduced from £409 991 to only £253 371, compared with an increase from £556 039 to £673 318 in the control district.

Even in the first year of a new community clinic programme, before many patients had gained access to the service, leg ulcer healing was improved and costs reduced.

Laboratory markers of carotid *versus* iliac–femoral atherosclerosis

A. D. Blann, M. Steiner* and C. N. McCollum, *Department of Surgery, University Hospital of South Manchester, Manchester, UK and *University of Rostock, Germany*

To dissect the role of inflammatory mediators and ischaemia–reperfusion injury of the vasculature and muscle groups in atherosclerosis, 98 patients with symptomatic disease of the iliac–femoral arteries alone, 37 with symptomatic disease of the carotids alone and 210 age- and sex-matched controls were studied. Plasma was obtained for measurement of the atherosclerosis marker von Willebrand factor (vWF) and adhesion molecules E-selectin (E-sel), intercellular adhesion molecule (ICAM) 1 and vascular cell adhesion molecule (VCAM) 1 by enzyme-linked immunosorbent assay.

	Control	Iliac–femoral	Carotid	*P* for trend*
vWF (units dl^{-1})	100(36)	135(39)†	133(35)†	$<0{\cdot}001$
E-sel (ng ml^{-1})	54(19)	57(21)	52(21)	0 421
ICAM-1 (ng ml^{-1})	288(92)	372(120)‡	310(103)	$<0{\cdot}001$
VCAM-1 (ng ml^{-1})	633(196)	655(228)	664(246)	0·659

Values are mean(s.d.). *Analysis of variance; †$P<0{\cdot}05$ *versus* control, ‡$P<0{\cdot}05$ *versus* control and carotid (Tukey's test)

There was no difference in raised levels of vWF or in normal levels of both E-sel and VCAM-1 between the patient groups and controls. However, ICAM-1 was raised only in those with iliac–femoral disease. One mechanism for this may be the repeated ischaemia–reperfusion cycles of walking, which would damage the endothelium and muscle beds in claudicants but not in those with carotid disease.

How important is the external carotid artery in patients with symptomatic carotid stenosis?

T. A. J. Calvey, A. J. McCleary, P. Braithwaite, A. Bodenham, A. I. D. Mavor, S. Homer-Vanniasinkam and M. J. Gough, *Vascular Surgical Unit, The General Infirmary at Leeds, Leeds, UK*

The contribution of the external carotid artery (ECA) to cerebral perfusion in patients undergoing carotid endarterectomy (CE) is considered by most to be insignificant. However, ECA endarterectomy may prevent transient ischaemic attacks (TIAs) in some patients with internal carotid artery (ICA) occlusion and thus its contribution to cerebral perfusion may be important.

CE, with sequential occlusion of the external (ECA) and common (CCA) carotid arteries, allows assessment of ECA-derived cerebral blood flow by measuring jugular bulb oxygen saturation (S_{JvO_2}) and cerebral haemoglobin saturation (HbO_2; niroscopy). In 51 patients undergoing CE, S_{JvO_2} and HbO_2 fell on clamping the ECA in 24 and 43 patients respectively (decrease in S_{JvO_2} from 78 3 (range 73–84) per cent to 70·7 (68–76) per cent *versus* 76·4 (68–86) per cent in those with no change, $P<0{\cdot}01$). In 14 of 24 there was a further decrease in S_{JvO_2} following CCA occlusion, whereas in 22 patients JvO_2s fell only when the CCA was clamped. In 15 patients with no reduction in S_{JvO_2} following the CCA clamp, ten had experienced a fall on ECA occlusion, thus suggesting that the ECA was responsible for a significant proportion of cerebral perfusion in these patients. In only two patients did S_{JvO_2} fall on ECA clamping without a corresponding fall in HbO_2 (regional oxygenation), indicating ischaemia beyond the sampling area of the niroscope. The falls in HbO_2 that occurred without changes in S_{JvO_2} in 19 patients after ECA occlusion are likely to represent alterations in extracranial perfusion.

These results indicate that the ECA makes a significant contribution to cerebral perfusion in almost 50 per cent of patients undergoing CE for critical ICA stenosis. Thus the ECA should be preserved carefully during CE, whereas ECA endarterectomy alone may be useful in selected patients with ICA occlusion.

Is patch angioplasty required for large arteries after carotid endarterectomy?

J. Golledge, R. Cuming, M. Ellis, A. H. Davies and R. M. Greenhalgh, *Department of Surgery, Charing Cross and Westminster Medical School, London, UK*

Routine patch angioplasty has been advocated following carotid endarterectomy to reduce the incidence of restenosis. This study assessed the effect of selective patching of smaller arteries on the rate of restenosis. Selection was based on intraoperative calliper measurement of the external distal internal carotid diameter.

Some 213 patients underwent carotid endarterectomy performed by one surgeon. Following endarterectomy a 5-mm Dacron (Du Pont, Stevenage, UK) patch was selectively employed for distal internal carotid arteries of less than 5 mm (group 1, 95 patients) or less than 6 mm (group 2, 118 patients). Forty-five patients (47 per cent) in group 1 and 72 (61 per cent) in group 2 received patch angioplasty. Patients were followed prospectively for a mean of 32 (group 1) and 12 (group 2) months with duplex scanning at 24 h, 1 week, 3, 6, 9 and 12 months, and yearly.

Life-table analysis with log rank testing revealed:

	Patch	No patch	*P*
Restenosis > 50 per cent (%)			
Group 1 (24 months)	14	24	0·4
Group 2 (12 months)	13	11	>0·5
Survival rate (%)			
Group 1 (24 months)	96	86	0·4
Group 2 (12 months)	100	93	>0·5
Stroke rate (%)			
Group 1 (24 months)	6	9	>0·5
Group 2 (12 months)	0	4	0·4

This study shows that when patch angioplasty is used selectively for distal internal carotid arteries with a diameter of less than 6 mm, equivalent outcome is achieved for patched and non-patched patients, while minimizing the requirement for patching.

CD11b expression in response to cancer cells spilled at laparotomy and laparoscopy

C. C. Nduka, J. F. Dye, L. Yong, A. O. Mansfield and A. W. Darzi, *Academic Surgical Unit, Imperial College School of Medicine at St Mary's Hospital, London, UK*

Although studies suggest that laparoscopy attenuates systemic postsurgical inflammatory and immune responses, the effect on local responses and the subsequent fate of intraperitoneal cancer cells is unknown. Port-site metastases suggest that factors specific to laparoscopy may facilitate the survival, implantation or growth of spilled tumour cells. A rat model was used to study postsurgical peritoneal and systemic leucocyte activation in the presence of syngeneic colonic cancer cells

Inbred male WAG rats were divided into three groups· laparotomy, laparoscopy and controls. Laparoscopy was performed with a 4-mm endoscope using carbon dioxide insufflated to 4 mmHg. Laparotomy was performed with a 5-cm midline incision. Following anaesthesia 1×10^6 CC531s cells were injected into the peritoneal cavity. After 1 h peritoneal lavage was performed to recover free peritoneal macrophages (PMs) and cancer cells, which were assessed blindly for viability by trypan blue exclusion. PM and peripheral blood mononuclear cell (PBMC) CD11b expression were assessed by flow cytometry.

	Control	Laparoscopy	Laparotomy
PBMC CD11b MCF	7·26(3·10)	8·76(5·39)	33·7(20·9)*
PM CD11b MCF	287(46·6)	252(51·6)	223(61·3)‡
Cancer cells ($\times 10^5$)	1·3(1·6)	3·1(2·8)	1·3(1·8)
PM cells ($\times 10^5$)	30·2(24·1)	62·2(16·3)†	49·4(20·9)

Values are mean(s.d.). MCF, mean channel fluorescence. $^*P < 0·01$ *versus* laparoscopy and control, $^†P < 0·01$ *versus* control (Kruskal–Wallis analysis of variance); $^‡P < 0·05$ *versus* control (Tukey–Kramer multiple comparisons test) ($n = 9$)

Laparotomy caused a significant systemic increase in mononuclear cell CD11b expression. However, laparoscopy abrogated the decrease in PM CD11b expression compared with laparotomy. The exact mechanism of this response is unknown, but this, in combination with the increased number of viable peritoneal cells recovered at laparoscopy, may influence subsequent cancer cell survival and seeding.

Hypoxia induces tumour necrosis factor α production by a human monocytic cell line

P. Tan, Y. C. Lim, S. Homer-Vanniasinkam and S. M. Parkin, *Vascular Surgical Unit, The General Infirmary at Leeds and Department of Biomedical Sciences, Bradford University, UK*

The pathogenesis of ischaemia–reperfusion injury (IRI) is not clearly understood although the pathophysiological manifestations of this condition (neutrophil recruitment, oedema and tissue necrosis) are similar to those seen in acute inflammation. Tumour necrosis factor (TNF) α is a pro-inflammatory cytokine and its concentration is raised in animal models of IRI. The effects of hypoxia and reoxygenation (to mimic ischaemia and reperfusion) on TNF release by human saphenous vein endothelial cells (HSVECs) and a human monocytic cell line, U937, were investigated.

To simulate ischaemia and reperfusion, HSVECs and U937 cells were incubated in a hypoxic atmosphere of 95 per cent nitrogen : 5 per cent carbon dioxide for 6 h and then reoxygenated in a normoxic atmosphere for up to 240 min. Controls were HSVECs and U937 cells that were not subjected to hypoxia. TNF in the hypoxic and reoxygenated supernatants was detected by a bioassay using the TNF-sensitive cell line, WEHI 164.

TNF was not detected in supernatants from HSVECs subjected to hypoxia or hypoxia–reoxygenation (less than 50 pg ml^{-1}). However, mean(s d.) TNF levels in the supernatant from U937 cells subjected to hypoxia (212·4(46·8) pg ml^{-1}, $P = 0·02$) were significantly raised compared with the control (52·1(12·1) pg ml^{-1}) TNF bioactivity in the U937 supernatants could be neutralized to 51·5(15·4) pg ml^{-1} ($P = 0·02$) with a polyclonal goat antihuman TNF antibody.

Hypoxia induces TNF release by U937 cells. The results suggest that TNF release by monocytes or tissue macrophages during ischaemia may be responsible for the initiation and continuation of the inflammatory response associated with IRI.

Inhibition of neutrophil migration at the site of infection increases remote organ neutrophil sequestration and injury

M. A. Mercer-Jones*†, W. G. Cheadle*, M. J. Hershman† and H. C. Polk Jr*, **Price Institute and VAMC, Department of Surgery, Louisville, Kentucky, USA and* †*Department of Surgery, Royal Liverpool University Hospital, Liverpool, UK*

Upregulation of the leucocyte β_2 integrin, CD18, is a key event in neutrophil–endothelial adhesion and neutrophil-mediated organ injury. Blocking CD18 with monoclonal antibodies reduces lung and liver neutrophil sequestration and injury in animal models of ischaemia–reperfusion or endotoxaemia. However, with a persistent septic challenge, interference with host leucocyte phagocytic defence could affect outcome adversely. The aim of this study was to assess the effect of blocking CD18 on the local and remote neutrophil responses, on bacteraemia, and on remote organ injury after faecal peritonitis.

Swiss Webster mice had sham caecal ligation and puncture (CLP) or received intravenous anti-CD18 antibody (1 mg kg^{-1}) or control immunoglobulin (Ig) G at the time of CLP and 12 h later. Some 18 h after CLP, lung and liver tissue neutrophil content were measured by myeloperoxidase (MPO) assay, peritoneal cells and blood were differentially counted, blood was cultured and serum aspartate aminotransferase (ASAT) concentration was measured.

	Sham	Control IgG	Anti-CD18
MPO liver (units per g)	0·2(0·1)	0·8(0·2)	3·9(0·5)*
MPO lung (units per g)	5·2(1·3)	11·4(3·0)	21·3(3·9)*
Blood neutrophils ($\times 10^6$ per ml)	1·0(0·1)	0·5(0·1)	1·2(0·1)*
Peritoneal neutrophils ($\times 10^6$ per mouse)	0·3(0·1)	10·0(0·4)	1·7(0·3)*
Blood aerobes (log c.f.u)	—	3·1(0·8)	5·0(0·4)*
Blood anaerobes (log c.f.u.)	—	3·3(0·8)	5·0(1·1)*
Serum ASAT (units per ml)	101·3(8·4)	194·2(19·9)	264·0(23·6)*

Values are mean(s.e.m) of six animals per group. c.f.u., colony-forming units. *$P < 0{\cdot}05$ *versus* control (t test and Mann–Whitney U test)

In a model of faecal peritonitis, blockade of CD18: (1) inhibits CD18-dependent neutrophil migration into the peritoneal cavity; (2) worsens bacteraemia; (3) increases neutrophil sequestration in the liver and lung, and (4) increases liver injury. Hence, interference with neutrophil trafficking to the site of infection may paradoxically increase neutrophil-mediated remote organ injury.

Role of lipopolysaccharide binding protein in acute pancreatitis

P. J. Erwin, H. Lewis, R. R. Schumann*, B. J. Rowlands and M. I. Halliday, *Department of Surgery, The Queen's University, Belfast, UK and *MDC, Berlin, Germany*

The acute-phase protein lipopolysaccharide binding protein (LBP) initiates lipopolysaccharide-activated cellular responses leading to the production of proinflammatory cytokines implicated in the pathogenesis of acute pancreatitis (AP). The authors sought to define the role of LBP, compared with interleukin (IL) 6 and C-reactive protein (CRP), as a marker of disease severity in AP.

Patients with AP ($n = 20$) were stratified using the modified Glasgow criteria into those with severe ($n = 7$) and mild ($n = 13$) disease. Plasma samples were collected on admission and at 24, 48 and 72 h. LBP was quantified by an enzyme-linked immunosorbent assay (ELISA) employing polyclonal goat anti-human LBP as the capture antibody and biotinylated anti-LBP for detection. Tumour necrosis factor (TNF) was measured by ELISA, IL-6 by bioassay (B9 cell line) and CRP using precipitin quantitation.

On admission, mean(s.d.) LBP concentrations in patients with AP were significantly increased (normal volunteers 7·7(2·9) μg ml^{-1} *versus* AP 17·4(1·8) μg ml^{-1}; $P = 0{\cdot}0001$ (Mann–Whitney U test). CRP and IL-6 concentrations were also raised and there was a positive correlation between LBP and CRP ($r = 0{\cdot}48$, $P < 0{\cdot}05$). Higher levels of LBP were associated with severity and this became significant by 72 h (severe 28·7(4·9) μg ml^{-1} *versus* mild 16·8(3·4) μg ml^{-1}, $P = 0{\cdot}02$). By comparison IL-6 concentrations were significant on admission (severe 615(310) pg ml^{-1} *versus* mild 0 pg ml^{-1}, $P = 0{\cdot}001$), whereas CRP levels peaked 24 h later (severe 155(31) mg l^{-1} *versus* mild 58(12) mg l^{-1}, $P = 0{\cdot}02$). There was then a steady decline in the concentration of these proteins. TNF was detected in only two samples.

This is the first demonstration that increased LBP concentrations correlate with disease severity in AP The importance of this protein in the progression to multiple organ dysfunction syndrome and death requires further study.

Intercellular adhesion molecule 1 is expressed on human polymorphonuclear neutrophils and is essential for both neutrophil adherence and aggregation

J. H. Wang, H. P. Redmond, D. M. Sexton, R. W. G. Watson, D. T. Croke and D. Bouchier-Hayes, *Department of Surgery, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland*

The adhesion system, intercellular adhesion molecule (ICAM) 1 and CD11/CD18, plays a critical role in neutrophil (PMN) attachment to and migration through endothelium, and subsequent PMN accumulation and organ injury during the systemic inflammatory response syndrome (SIRS). However, it remains unknown whether this adhesion system is involved in PMN–PMN interaction and subsequent PMN clumping in the microcirculation as evidenced during SIRS.

To determine this, human PMNs were obtained from healthy donors and isolated by density gradient to undergo the following experiments. For the first step the authors investigated whether ICAM-1 was expressed on normal human PMNs and whether this expression was upregulated by lipopolysaccharide (LPS; 25 ng ml^{-1}) and tumour necrosis factor (TNF; 10 ng ml^{-1}) by employing flow cytometry and reverse transcription–polymerase chain reaction (RT–PCR). Second, they examined whether ICAM-1 expression on human PMNs was essential for PMN–PMN adherence and aggregation by using ICAM-1 monoclonal antibody (M532; 30 μg ml^{-1}) and CD11b monoclonal antibody (M551; 20 μg ml^{-1}).

Normal human PMNs were found to express ICAM-1 with approximately 90 per cent positive cells; this expression was augmented by LPS and TNF stimulation following 1, 6, 12, 18 and 24 h of incubation ($P < 0{\cdot}05$ *versus* medium). The presence of ICAM-1 messenger RNA in human PMNs was further detected by RT–PCR before and after LPS and TNF treatment. Incubation of PMNs with LPS and TNF resulted in a significant increase in PMN–PMN adherence and aggregation ($P < 0{\cdot}05$ *versus* medium) Application of ICAM-1 monoclonal antibody could significantly attenuate LPS- and TNF-mediated PMN–PMN adherence and aggregation, by 40 and 68 per cent respectively ($P < 0{\cdot}05$ *versus* LPS and TNF only). Similar results were found in CD11b monoclonal antibody-treated group (53 per cent inhibition in PMN–PMN adherence and 76 per cent inhibition in PMN aggregation, $P < 0{\cdot}05$ *versus* LPS and TNF only).

These findings demonstrate for the first time that ICAM-1 is expressed on human PMNs, and that the interaction between ICAM-1 and CD11/CD18 may be the molecular basis for PMN–PMN interaction and PMN clumping in the microcirculation during SIRS.

Tumour-induced endotoxin sensitivity is associated with alterations in spleen cell tumour necrosis factor production and lymphocyte reactivity, but not interleukin 6 production

P. Renshaw, S. Fielden, O. Eremin and D. B. Gough, *Department of Surgery, University of Aberdeen Medical School, Aberdeen, UK*

The state of cancer is associated with an increased susceptibility to sepsis. Serum levels of tumour necrosis factor (TNF) and interleukin (IL) 6 (thought to be important mediators of sepsis) are frequently raised in patients with cancer while lymphocyte reactivity is reduced, but the relative contribution of each of these abnormalities to the development of sepsis is unclear. The aim of this study was to examine patterns of *in vitro* spleen cell TNF and IL-6 production (baseline and endotoxin-stimulated (5 μg *Escherichia coli*)) and lymphocyte reactivity in response to concanavalin (Con) A (1·25 μg ml^{-1}), and to relate these findings to the effect of *in vivo* endotoxin (75 μg *E coli*) on survival (4 days) in an animal tumour model.

Four groups of ten male C57/BL6 mice each were inoculated (hind limb) with LL2 tumour cells (1×10^5) or culture medium. At day 22, two groups (tumour and controls) were killed, spleen cells were isolated, and basal and endotoxin-stimulated TNF and IL-6 production were assessed (by enzyme-linked immunosorbent assay) as well as responses to Con A (incorporation of tritiated thymidine in c.p.m.). A further two groups (tumour and control) were challenged with endotoxin (75 μg *E. coli*) and survival was assessed for 4 days.

	Tumour	Control	P
Basal TNF secretion (pg ml^{-1})	361(8)	523(22)	<0·0005*
Stimulated TNF secretion (% increase)	871(25)	322(27)	<0·0005*
Basal IL-6 secretion (pg ml^{-1})	150(56)	173(62)	n.s.*
Stimulated IL-6 secretion (% increase)	1384(438)	1350(246)	n.s.*
Con A response (c.p.m.)	15 820(801)	21 090(845)	<0·0005*
Survival following endotoxin (%)	0	100	<0·0005†

Values are mean(s.e.m.). *Student's t test; †log rank test

The presence of tumour was associated with increased *in vivo* sensitivity to endotoxin, reduced basal and increased TNF secretion in response to *in vitro* endotoxin, reduced Con A responses, but normal basal and endotoxin-stimulated IL-6 secretion. Changes in spleen TNF production and lymphocyte reactivity, but not in IL-6 production, may be related to reduced resistance to sepsis in this animal tumour model.

Effects of polyadenylic–polyuridylic acid on human peripheral blood lymphocyte proliferation and activation

A. L. Khan, S. Fielden, S. D. Heys, F. Larsen* and O. Eremin, *Department of Surgery, University of Aberdeen, Aberdeen and *Ipsen International, London, UK*

Immune reactivity is a complex process incorporating cell activity, proliferation and differentiation. Polyadenylic–polyuridylic acid (PAPU), a synthetic polyribonucleotide, stimulates the cytotoxicity of defined subsets of cells involved in natural cytotoxicity but its effects on lymphocyte subset proliferation are less well documented. The aim of this *in vitro* study was to determine the effects of PAPU (1, 100 and 500 $\mu\text{g ml}^{-1}$) on concanavalin (Con) A (16·5 $\mu\text{g ml}^{-1}$), pokeweed mitogen (PWM) (4 $\mu\text{g ml}^{-1}$) and phytohaemagglutinin (PHA) (4 $\mu\text{g ml}^{-1}$) stimulated $[^3\text{H}]$thymidine incorporation into human peripheral blood lymphocytes (PBLs).

Blood was collected from ten volunteers and the PBLs separated on ficoll-hypaque and cryopreserved until use. The PBLs (2×10^5 cells per ml) were incubated *in vitro* with the three mitogens after preincubation with different concentrations of PAPU for 48 h. All concentrations of PAPU tested inhibited the response to mitogens used, compared with controls (no PAPU). The results are expressed as stimulation indices ($[^3\text{H}]$thymidine incorporation in the presence of mitogen/$[^3\text{H}]$thymidine incorporation in the absence of mitogen) (see *Table*).

Dose ($\mu\text{g ml}^{-1}$)	Con A	PWM	PHA
Control	45 (25–63)	18 (10–25)	61 (42–97)
1	24 (10–44)*	10 (3–20)*	39 (31–55)*
100	22 (12–43)*	9 (3–13)*	33 (11–50)*
500	10 (6–28)*	9 (5–25)*	32 (15–55)*

Values are median (interquartile range). *$P<0·05$ (within-group analysis, Wilcoxon matched pair test)

Soluble interleukin 2 receptor (sIL-2R) (a marker of T lymphocyte activation) was measured in the supernatant of *in vitro* cultured PBLs by enzyme-linked immunosorbent assay. PAPU (1, 100 and 500 $\mu\text{g ml}^{-1}$) increased the concentration of sIL-2R to 121, 131 and 164 pg ml^{-1} respectively, compared with controls (94 pg ml^{-1}). An understanding of these differential biological processes is important in producing protocols for immunotherapeutic regimens in humans.

Manipulation of septic and acute-phase responses with human recombinant growth hormone and insulin-like growth factor 1

K. Mealy, A. Clooney, J. Jackson, P. Marks and T. P. J. Hennessy, *Department of Immunology, St James's Hospital and Dublin Institute of Technology, and Department of Surgery, Trinity College and St James's Hospital, Dublin, Ireland*

The acute-phase response is an important adaptive response to sepsis. Because human recombinant growth hormone (hrGH) increases skeletal muscle protein synthesis in sepsis, it was postulated that hrGH would also increase hepatic acute-phase protein synthesis.

Male Wistar rats were treated with hrGH (2·5 units kg^{-1} day^{-1}; $n=31$) or insulin-like growth factor (IGF) 1 (4 mg kg^{-1} day^{-1}, $n=32$) for 24 or 48 h following caecal ligation and puncture (CLP). Sham ($n=23$) and CLP alone ($n=23$) groups acted as controls. The animals were killed and blood was taken for a full blood count, total protein (measured by refractometry), albumin and α, β and γ globulins (measured by electrophoresis and which contain the major acute-phase proteins in the rat). Food intake and change in body-weight were recorded throughout the study. Values are mean(s.e.m.) for combined 24- and 48-h data.

Group	Weight change (g)	Total protein (g l^{-1})	Albumin (g l^{-1})	Deaths
Sham	+3·6(1·6)	50·5(1·7)	22·6(1·3)	0 of 23
CLP alone	−12·7(2·2)*	50·0(2·6)	21·6(1·7)	5 of 28*
CLP plus hrGH	−11·2(1·4)*	45·0(1·8)	17·5(0·9)†	2 of 33
CLP plus IGF-1	−13·9(1·6)*	43·4(2·4)	17·5(1·1)†	5 of 35

*$P<0·05$ *versus* sham, †$P<0·05$ *versus* sham and CLP alone (analysis of variance)

Mortality was significantly increased only in the CLP alone group. Food intake and weight loss were similar in all CLP groups; however, total protein and albumin levels fell with hrGH and IGF-1 treatment in comparison with both CLP alone and sham groups. hrGH and IGF-1 did not increase levels of α_1, α_2 or β globulins.

hrGH and IGF-1 may improve survival but do not increase acute-phase response in this rat model of sepsis.

Lipopolysaccharide in air may account for acceleration of tumour growth after laparotomy

M. L. Da Costa, H. P. Redmond and D. Bouchier-Hayes, *Department of Surgery, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland*

The authors have previously shown that laparotomy and laparoscopy differentially accelerate tumour growth. The aim of this study was to evaluate the effect of laparotomy, laparoscopy and lipopolysaccharide (LPS) on tumour growth in a murine model.

In study 1, C57BL/6 female mice ($n=60$) received right flank injections of 1×10^6 B16 melanoma cells. When tumours became palpable the animals were randomized into control (anaesthetic only), laparoscopy, laparotomy, air laparoscopy, near laparotomy and intraperitoneal LPS (45 ng given at day 0) groups.

In study 2, tumour-bearing C3H/HeN (LPS-sensitive) and C3H/HeJ (LPS-resistant) mice ($n = 10$ in each group) underwent the former three procedures. In both studies the tumours were measured and flank tumour volume (FTV) was calculated every other day for 10 days thereafter.

	DDFTV per cm^3 (study 1)		
	Day 2	Day 4	Day 10
Control	0·08(0·015)	0·18(0·036)	0·29(0·035)
Laparotomy	0·34(0·049)*‡§	0·43(0·054)*†‡	0·45(0·035)*†‡
Laparoscopy	0·25(0·023)*	0·20(0·023)	0·27(0·031)
Near laparotomy	0·20(0·033)*	0·27(0·048)	0·34(0·027)
Air laparoscopy	0·40(0·067)*†‡§	0·39(0·045)*†‡	0·42(0·039)*†
LPS	0·23(0·023)*	0·41(0·024)*†‡	0·44(0·048)*†

Values are mean(s.e.m.). DDFTV, delta difference flank tumour volume. *$P < 0\cdot05$ *versus* control, †$P < 0\cdot05$ *versus* laparoscopy, ‡$P < 0\cdot05$ *versus* near laparotomy, §$P < 0\cdot05$ *versus* LPS (analysis of variance)

In study 2, DDFTV per cm^3 for laparotomy HeN was significantly greater than that for control HeN, control HeJ, laparotomy HeJ, and laparoscopy HeN and HeJ ($P < 0\cdot0005$) at days 2 and 4 after operation.

This study demonstrates a significant increase in FTV following laparotomy, laparoscopy, near laparotomy, air laparoscopy, and LPS compared with the control at 2 days after operation. The increase then became significant in the laparotomy, air laparoscopy and LPS groups compared with the control and laparoscopy at day 4. Over the next 4 days there was no significant increase in FTV between the groups; however at day ten, there was a further significant increase in FTV in the laparotomy, air laparoscopy and LPS groups compared with the control and laparoscopy. Study 2 showed a significant increase in tumour growth in the LPS-sensitive C3H mice compared with the LPS-resistant strain after laparotomy compared with that in all groups.

Thus it appears that exposure of the peritoneal cavity to LPS present in small concentrations, as encountered in room air, stimulates tumour growth either directly or indirectly during the early postoperative period. There also appears to be a second phase of increased growth after 8 days, due to as yet unidentified factors.

Activation of adult human vascular endothelium after brief periods of hypoxia

P. Tan, Y. C. Lim, S. M. Parkin, M. J. Gough and S. Homer-Vanniasinkam, *Vascular Surgical Unit, The General Infirmary at Leeds and Department of Biomedical Sciences, University of Bradford, UK*

Peripheral blood neutrophils (PMNs) recruited to postischaemic skeletal muscle during reperfusion induce tissue injury. PMN adherence to activated vascular endothelium is mediated by endothelial cell adhesion molecules (CAMs) such as E-selectin. This study aimed to define the role of E-selectin in mediating PMN adhesion after brief periods (1–2 h) of hypoxia followed by reoxygenation.

Human saphenous vein endothelial (HSVE) cells were isolated, cultured to confluence and then subjected to hypoxia (95 per cent nitrogen : 5 per cent carbon dioxide) in a specialized incubator, followed by reoxygenation (95 per cent air : 5 per cent carbon dioxide), and then immunoassayed for CAM expression.

Two hours of hypoxia induced small but significant increases in E-selectin expression above the control (mean(s.e.m.) 32(11) per cent, $P = 0\cdot03$; 85(20) per cent, $P = 0\cdot003$; 79(9) per cent, $P = 0\cdot0001$, after 2, 4 and 6 h reoxygenation respectively. One hour of hypoxia induced 26(17) per cent ($P = 0\cdot19$), 54(12) per cent ($P = 0\cdot007$), and 41(17) per cent ($P = 0\cdot06$) rises in E-selectin expression above the control value after 2, 4 and 6 h of reoxygenation respectively. Six hours of hypoxia without reoxygenation induced a 52(16) per cent ($P = 0\cdot02$) rise in E-selectin expression. Intercellular adhesion molecule (ICAM) 1 expression was constitutively high in HSVE cells.

PMN adhesion assays were then performed under rotational conditions using Mg^{2+}-free medium. Some 10·5(1·2) PMNs per high-power field (h.p.f.) ($P = 0\cdot001$)) were adherent to HSVE cells subjected to 2 h of hypoxia and 4 h of reoxygenation, compared with 0·18(0·1) PMNs per h.p.f. (negative control) and 40·2(3·0) PMNs per h.p.f. (4 h activation) The increased adhesion seen after hypoxia–reoxygenation was significantly reduced by an anti-E-selectin monoclonal antibody (3·9(0·8) PMNs per h.p.f., $P = 0\cdot001$), confirming E-selectin mediated adhesion.

In conclusion, brief periods of hypoxia followed by reoxygenation induced endothelial activation and E-selectin expression, resulting in increased PMN recruitment. Blockade of E-selectin may reduce PMN recruitment and PMN-mediated injury during reperfusion following brief periods of ischaemia.

Which is the most appropriate quality-of-life analysis tool in patients with lower limb ischaemia?

I. C. Chetter, J. I. Spark, D. J. A. Scott and R. C. Kester, *Department of Vascular and Endovascular Surgery, St James and Seacroft University Hospitals, Leeds, UK*

In this era of evidence-based medicine and limited resources there is an obligation on clinical and economic grounds, to demonstrate that not only patient survival but also the quality of patients' lives is improved. This study aimed to determine whether increasing lower limb ischaemia is associated with a reduction in quality of life (QOL) and which of three commonly used generic QOL instruments is most suitable for use in patients with lower limb ischaemia in terms of validity, reliability and responsiveness.

Some 165 patients (100 men and 64 women of median age 69 (range 41–87) years were graded according to International Society of Cardiovascular Surgery suggested reporting standards (i.e. seven mild, 79 moderate and 15 severe claudicants, 26 patients had rest pain and 38 tissue loss.) Patients completed Short Form 36 (SF36), EuroQol (EQ) and Nottingham Health Profile (NHP) questionnaires at interview. Kruskal-Wallis analysis of variance detected QOL changes across the whole group. Correlation between similar domains measured by the three instruments reflected convergent validity. A subgroup of 80 patients completed additional copies of questionnaires before attendance. Correlation between the two sets of responses reflected test–retest reliability. Spearman rank correlation assessed validity and reliability The instrument's ability to distinguish QOL differences between individual grades of lower limb ischaemia (Mann–Whitney U test) reflected responsiveness.

Increasing lower limb ischaemia conferred significant ($P < 0\cdot01$) deterioration in: (1) SF36-measured physical functioning, physical role, pain, vitality and social functioning; (2) EQ-measured mobility, self-care, usual activities, pain and anxiety/depression; and (3) NHP-measured energy, pain, emotional reaction, sleep, social isolation and physical mobility. All three instruments were significantly valid and reliable ($r_S > 0\cdot7$). The validity of SF36 and NHP ($r_S = 0\cdot63$–$0\cdot78$) was superior to that of EQ ($r_S = 0\cdot42$–$0\cdot7$). SF36 was most responsive to changes in mobility, pain and social functioning. NHP was most responsive to mood changes.

QOL deteriorates with increasing lower limb ischaemia; this may add to the justification for the increased efforts and expenditure in the treatment of critical ischaemia. SF36 would appear to be the most appropriate generic QOL analysis tool (of those analysed) for use in patients with lower limb ischaemia. It may also provide a benchmark against which other generic and disease-specific instruments can be gauged.

Neutrophil activation and severity of peripheral vascular disease

U. J. Kirkpatrick, M. Mossa, S. Nassar and C. N. McCollum, *Department of Surgery, University Hospital of South Manchester, Manchester, UK*

Neutrophils are activated within 15 min after exercise in patients with intermittent claudication. The earlier systemic changes after exercise were examined in 33 patients with claudication who had rested for at least 1 h. Neutrophil activation was assessed by flow cytometric measurement of hydrogen peroxide generation.

The expected leucocytosis following exercise reached a peak 5 min after exercise and returned to baseline by 15 min ($P < 0\cdot001$, repeated analysis of variance) Looking at the patients with claudication as a whole, there appeared to be no consistent change in neutrophil activation after exercise between samples taken at rest and at 5 min after maximal exercise. However, a more detailed examination revealed a surprising result The patients could be divided into groups depending on whether sampled neutrophil activation increased or decreased at 5 min after maximal exercise. The baseline activation can also be correlated with the mean ankle:brachial pressure index (ABPI) ($r = -0\cdot416$, $P < 0\cdot02$).

	Neutrophil activation at 5 min		
	Increased	Decreased	P*
Change in activation after exercise (%)			
15 min	35 (−8 to 94)	−22 (−48 to 1)	<0·002
30 min	42 (−19 to 72)	−22 (−40 to 3)	<0·01
Mean ABPI	1·57 (1·40–1·66)	1·32 (1·23–1·54)	<0·01

Values are median (interquartile range). *Mann–Whitney *U* test

Claudicants with similar symptoms comprise a heterogeneous group in terms of biochemical changes Patients with more severe disease, i.e. lower ABPI, have more activated neutrophils which are lost to sampling after exercise, implying neutrophil adherence.

Constitutive nuclear κB expression is a marker for neutrophil activation and multiple organ failure in thoracoabdominal aortic aneurysm repair

N. J. Cheshire, S. Foulds and A. O. Mansfield, *Academic Surgical Unit, Imperial College of Medicine at St Mary's Hospital, London, UK*

It has recently been shown that polymorphonuclear neutrophils (PMNs) are activated during visceral reperfusion in thoracoabdominal aortic aneurysm (TAAA) repair and that activation is associated with the postoperative development of systemic complications and multiple organ failure Furthermore, peak neutrophil CD11b adhesion receptor expression has been shown to be preceded by a rise in plasma endotoxin levels, suggesting translocation of bacterial endotoxin from the ischaemic gut. The activation of PMNs by endotoxin is mediated by the intracellular transcription factor nuclear factor κB (NFκB). It has recently been reported that *in vitro* NFκB inhibition in healthy neutrophils abrogates the stimulatory effects of plasma from patients undergoing TAAA repair. NFκB regulates a variety of cellular processes important in the systemic inflammatory response and is mobilized to the nucleus upon stimulation by endotoxin as well as a number of other stimuli and may therefore be central in PMN activation during visceral reperfusion. This study investigated the relationship between changes in neutrophil NFκB activation during TAAA repair and postsurgical outcome.

Venous blood samples were taken before operation and at 10-min intervals during operation in 11 patients undergoing TAAA repair. Five patients recovered from the operation without developing any complications and six developed both renal and respiratory failure. PMN nuclear NFκB expression was measured by a novel flow cytometric assay. Perioperative nuclear NFκB activity in these two groups was as follows

	Preop.	30 min after aortic cross-clamping	Time after visceral reperfusion (min) 0	10	30	60
Uncomplicated	128(22)	141(31)	137(55)	134(43)	119(18)	123(8)
Complicated	241(46)	311(32)	253(9)	191(54)	292(29)	191(30)

Values are mean(s.e.m.). $P = 0\cdot0024$ (analysis of variance)

In addition, preoperative neutrophil NFκB correlated with peak intraoperative neutrophil CD11b expression ($r = 0\cdot826$). These results show that NFκB expression rises during TAAA repair; this rise is significantly greater in patients who subsequently develop complications and occurs in a pattern similar to that reported for intraoperative PMN CD11b changes, although peak NFκB levels occur earlier and there is a marked difference in constitutive nuclear NFκB activity between the two groups ($P = 0\cdot012$, Student's *t* test). Constitutive PMN nuclear NFκB levels identify patients susceptible to PMN activation and multiple organ failure after TAAA reconstruction.

Ischaemia depletes antioxidant capacity, which is exacerbated by reperfusion

J. I. Spark, L. Gallivan, I. C. Chetter, R. C. Kester, P. J. Guillou and D. J. A. Scott, *Department of Vascular Surgery, St James's University Hospital, Leeds, UK*

It was hypothesized that ongoing ischaemia depletes the body's total antioxidant capacity (TAC) These antioxidant defence systems are essential to protect the body from the reactive oxygen species that are released following reperfusion. A consequence of this is development of the ischaemia–reperfusion syndrome and sepsis. This study aimed to examine the TAC of patients with chronic critical leg ischaemia undergoing femorodistal bypass, and to correlate this with lipid peroxidation (endothelial damage), changes in capillary permeability and clinical outcome.

Some 15 patients (nine men and six women of median age 71 (range 62–79) years) with a median duration of ischaemia of 6 weeks and ten matched controls were studied. Peripheral venous blood was taken before operation and during reperfusion. Assays were performed for malondialdehyde (MDA, a product of lipid peroxidation) and TAC. Changes in capillary permeability were measured by changes in the urinary albumin:creatinine ratio (ACR) following reperfusion of the ischaemic leg and expressed as a percentage increase from the control value. Clinical outcome in terms of sepsis and the systemic inflammatory response syndrome (SIRS) was recorded

	MDA (μmol l^{-1})		TAC (μmol l^{-1})		Increase in ACR (%)	
	Controls	Patients	Controls	Patients	Controls	Patients
Preop	0·25 (0·02–0·7)	0·6 (0·3–0·9)*†	860 (730–890)	490 (440–940)‡§	0·1	5·3 (2·1–9·9)†‡
1 h reperfusion	—	1·4 (0·8–1·59)	—	230 (210–295)	—	305 (75–668)

Values are median (interquartile range) *$P < 0\cdot05$, ‡$P < 0\cdot01$ *versus* control, †$P < 0\cdot01$, §$P < 0\cdot05$ *versus* 1 h reperfusion (Mann–Whitney *U* test)

Patients who went on to develop SIRS had a significantly lower TAC with a corresponding greater increase in MDA and ACR

Chronic ischaemia results in depletion of the TAC, which is further exacerbated by reperfusion. Vascular patients with a lower TAC develop increased capillary permeability as a result of ischaemia–reperfusion, which can ultimately progress to SIRS. It should be possible to augment their defence with exogenous antioxidants.

Management of preoperative coagulopathy in ruptured abdominal aortic aneurysm

T. Whittlestone, S. Hadjikoutis, R. N. Baird and P. M. Lamont, *Vascular Studies Unit, Bristol Royal Infirmary, Bristol, UK*

Preoperative coagulopathy is known to correlate with poor outcome following rupture of an abdominal aortic aneurysm (AAA). This study aimed to assess how closely the perioperative transfusion of platelets and fresh frozen plasma matched the severity of preoperative coagulation deficits in a series of 105 patients with ruptured AAA.

The 30-day mortality rate in this series was 36 per cent. The results of the preoperative coagulation screen taken on admission to hospital were compared with the number of units of blood and blood products given to patients in the perioperative period. Clinical, anaesthetic and resuscitation room records were checked against Blood Transfusion Service records to ensure accuracy.

The mean preoperative INR in survivors was 1·3 (range 1·0–1·7) compared with 1·8 (range 1·3–2·6) in non-survivors. The mean platelet count in survivors was 161 (range 123–421) $\times 10^9$ l^{-1} compared with 86 (range 52–371) $\times 10^9$ l^{-1} in non-survivors. These differences were significant ($P<0·001$, Wilcoxon rank sum test). A subset of 12 patients with severe coagulopathy (INR greater than 2 and platelet count below 80×10^9 l^{-1}) had a perioperative mortality rate of 92 per cent. There was no correlation between the degree of coagulopathy and the number of units of platelets and fresh frozen plasma transfused. No significant difference was found between survivors and non-survivors in the mean number of units of platelets (2·9 *versus* 3·2) and fresh frozen plasma (3·3 *versus* 4·1) transfused.

Clotting abnormalities in patients with ruptured AAAs are poorly managed. More aggressive management may help to reduce the mortality rate from this condition.

Bowel ischaemia in thoracoabdominal aortic aneurysm surgery is associated with significant endotoxaemia and oxidative stress

H. Hafez, C. Berwanger, L. Hadjinikolaou, B. Richmond, J. Wolfe, A. Mansfield and G. Stansby, *Academic and Regional Vascular Unit, Imperial College School of Medicine at St Mary's Hospital, London, UK*

Surgery for thoracoabdominal aortic aneurysm (TAAA) carries higher morbidity and mortality rates than that for abdominal aortic aneurysm (AAA). One possible reason is the magnitude of endotoxaemia and oxidative stress following bowel ischaemia–reperfusion in TAAA surgery.

Some 15 patients undergoing routine TAAA surgery types III and IV and ten control patients undergoing routine AAA surgery were studied. Sigmoid tonometry was used to measure sigmoid mucosal pH ($\mathrm{pH_i}$) at seven time-points (incision, clamp on, clamp off, 1, 4, 8 and 24 h after declamping). Heparinized arterial blood samples were collected at the same time-points and assayed for endotoxin levels and total antioxidant concentrations.

Mean(s.e.m.) $\mathrm{pH_i}$ was similar in both groups at incision. During surgery, $\mathrm{pH_i}$ dropped significantly more for TAAA than for AAA (6·87(0·03) *versus* 7·12(0·06); $P<0·05$, analysis of variance. Mean(s.e.m.) peak plasma endotoxin level was 112(48) pg $\mathrm{ml^{-1}}$ for TAAA and 36(13) pg $\mathrm{ml^{-1}}$ for AAA ($P<0·05$, Mann–Whitney *U* test). Plasma total antioxidant levels showed no significant changes during AAA surgery, but levels for TAAA dropped significantly from a baseline value of 1·40(0·02) mmol l^{-1} to 1·19(0·04) mmol l^{-1} at declamping and 1·24(0·05) mol l^{-1} after 1 h ($P<0·05$, Mann–Whitney *U* test at both points), thus indicating a significant oxidative stress following bowel reperfusion. Patients with $\mathrm{pH_i}$ lower than 7 had more significant endotoxaemia, antioxidant deficiency and a higher incidence of major complications (death, renal failure and prolonged ventilation) than those with $\mathrm{pH_i}$ above 7 ($P<0·05$).

Unlike AAA surgery, TAAA surgery is associated with significant endotoxaemia and oxidative stress. Adopting measures to ameliorate these changes may improve outcome in patients with TAAA.

Thermal preconditioning protects against ischaemia–reperfusion-induced lung injury

M. Javadpour, C. J. Kelly, M. Arumugasamy, A. Leahy and D. J. Bouchier-Hayes, *Department of Surgery, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland*

Lower torso ischaemia and reperfusion results in an acute lung injury, in part mediated by activated neutrophils. Thermal preconditioning describes the process whereby hyperthermia induces transient resistance of stressed cells to subsequent episodes of oxidative stress. The aim of this study was to determine whether thermal preconditioning before limb revascularization would have a protective effect on neutrophil-mediated lung injury in a model of aortic occlusion (30 min) and reperfusion (120 min).

Sprague Dawley rats were randomized into control ($n=7$), ischaemia–reperfusion (IR) ($n=7$) and IR treated with hyperthermia (HIR, $n=7$) groups (core body temperature was raised to 41 ± 0·5°C for 15 min, 18 h before IR insult). Pulmonary endothelial permeability was measured by wet to dry weight ratio (W : D) and bronchoalveolar lavage protein $\mathrm{BAL_{prot}}$ concentration. Lung neutrophil infiltration was determined by tissue myeloperoxidase activity (MPO) and bronchoalveolar lavage neutrophil count (BAL PMN). Lung injury was documented by histology.

	Control	IR	HIR
W.D	3·73(0·13)	4·06(0·3)†	3·57(0·2)§
$\mathrm{BAL_{prot}}$ (μg $\mathrm{ml^{-1}}$)	211·9(53·9)	821·7(443·2)*	305·8(74·5)§
MPO (units $\mathrm{g^{-1}}$)	1·42(0·89)	3·83(1·42)*	2·15(1·09)§
BAL PMN (10^5 $\mathrm{ml^{-1}}$)	0·57(0·37)	3·57(0·89)*	1·07(0·45)‡

Values are mean(s.e.m.). *$P<0·005$, †$P<0·05$ *versus* control; ‡$P<0·005$, §$P<0·05$ *versus* IR (Student's *t* test)

IR resulted in a significant increase in tissue oedema (W : D), $\mathrm{BAL_{prot}}$ concentration and evidence of tissue damage on histology. In addition, there was a marked increase in tissue neutrophil infiltration (MPO, BAL PMN). Preconditioning with hyperthermia significantly reduced tissue oedema and damage. This was associated with a reduction in tissue neutrophil infiltration These data indicate that thermal preconditioning protects against IR injury, possibly by decreasing neutrophil-mediated tissue injury.

Circulating adhesion molecules are consumed during ischaemia

U. J. Kirkpatrick, A. Blann, R. Adams and C. N. McCollum, *Department of Surgery, University Hospital of South Manchester, Manchester, UK*

Ischaemia–reperfusion injury causes important clinical effects in vascular surgery. *In vitro*, inflammatory stimuli upregulate intercellular adhesion molecule (ICAM) 1 but L-selectin is downregulated.

The response of these molecules to ischaemia was investigated in forearm vein blood from 20 volunteers undergoing tourniquet-induced forearm ischaemia over 10 min with 5- and 15-min reperfusion. Thromboxane concentration, white : red cell ratio, white cell hydrogen peroxide generation by flow cytometry; and serum levels of the cell adhesion molecules ICAM and L-selectin were compared with values obtained during forearm oxygen saturation by near-infrared spectroscopy

Hydrogen peroxide release, serum ICAM and L-selectin levels decreased during ischaemia despite a constant white : red cell ratio. The falls in neutrophil hydrogen peroxide generation correlated with severity of hypoxia ($r=0\cdot 563$, $P<0\cdot 03$). On reperfusion, hydrogen peroxide production and the level of ICAM recovered but that of L-selectin did not.

	Baseline	10-min ischaemia	5-min reperfusion	15-min reperfusion
White red cell ratio (×1000)	1·44(0·09)	1·47(0·09)	1·38(0·09)†	1·41(0·10)
White cell hydrogen peroxide release (MFI)	0·91(0·07)	0·77(0·09)*	0·85(0·10)	0·83(0·09)
Thromboxane (pg ml^{-1})	27(7)	99(14)*	69(17)*	51(9)
Serum ICAM (mg ml^{-1})	234(16)	207(17)*	228(19)	244(19)
Serum L- selectin (mg ml^{-1})	963(74)	843(47)*	826(38)*	816(49)*

Values are mean(s.e.m.) MFI, mean fluorescence intensity. *$P<0\cdot 05$ *versus* baseline; †$P<0\cdot 05$ *versus* ischaemia (repeated analysis of variance)

Sampled leucocyte activity falls during ischaemia as white cells adhere L-selectin concentration is not merely a reflection of leucocyte activation, but appears to be consumed in the binding of leucocytes to the endothelium during and following ischaemia.

Breast cancer bone metastases specifically express parathyroid hormone-related protein and its receptor

S. E. Downey, J. A. Hoyland*, A. J. Freemont* and N. J. Bundred, *Department of Surgery, University Hospital of South Manchester and *Department of Osteoarticular Pathology, University of Manchester, Manchester, UK*

Parathyroid hormone-related protein (PTHrP), an osteolytic factor secreted by osteoblasts and tumour cells, is reported to predispose to bone metastasis. To determine whether expression of PTHrP or its receptor specifically enhances tumour cell survival in bone, their expression was studied in primary breast cancers and breast cancer metastases in bone and lung.

In situ hybridization was used to identify the messenger RNA (mRNA) for both PTHrP and its receptor. The complementary DNA (cDNA) probes were labelled with ^{35}S and control slides treated with crude RNAse. Tumours were scored by two independent observers using the product of intensity of signal (1–3) and number of positive tumour cells (1, less than 20 per cent; 2, 20–80 per cent; 3, more than 80 per cent).

	PTHrP expression				
	Receptor mRNA	Median score	Protein mRNA	Median score	Both mRNAs
Breast cancer	99 of 107 (93)	3	26 of 29 (90)	3	26 (90)
Bone metastasis	33 of 33 (100)	6	11 of 12 (92)	6	11 (92)
Lung metastasis	8 of 15 (53)	2	8 of 15 (53)	2	5 (33)

Values in parentheses are percentages

Levels of PTHrP and its receptor mRNA were significantly higher in bone metastases than in primary breast carcinoma (protein, $P=0\cdot 038$; receptor, $P=0\cdot 0008$) but significantly lower in lung metastases (protein, $P=0\cdot 0027$, receptor, $P=0\cdot 0003$). Osteoblasts in bone metastases overexpressed PTHrP mRNA compared with normal bone.

Overexpression of both PTHrP and its receptor in breast cancer cells produces site-specific metastasis in bone due to autocrine–paracrine growth stimulation by PTHrP.

Relaxation training and imagery enhance quality of life during chemotherapy for breast cancer

L. G. Walker, M. B. Walker, E. Simpson, K. Ogston, A. Segar, S. D. Heys, A. K. Ah-See, A. W. Hutcheon, T. K. Sarkar and O. Eremin, *Behavioural Oncology Unit and Department of Surgery, University of Aberdeen Medical School, Aberdeen, UK*

Ninety-six women with locally advanced breast cancer took part in a prospective randomized clinical trial to evaluate the effects of relaxation therapy and guided imagery on quality of life. Forty-eight were randomized to the experimental treatment and 48 to the control condition. Patients received six cycles of neoadjuvant combination chemotherapy every 3 weeks followed by surgery (lumpectomy or mastectomy), tamoxifen and 20 fractions of radiotherapy.

Patients were taught relaxation using a combination of live training and audiocassette recordings and they were given a portfolio of ten coloured cartoons depicting natural killer cells destroying tumour cells for imagery during relaxation. They were asked to keep detailed daily records and these showed that 51 per cent practised at least once daily during chemotherapy.

Quality of life data were analysed by means of multivariate analysis of variance for repeated measures. When the Hospital Anxiety and Depression Scale and Rotterdam Symptom Checklist (RSCL) data were analysed on an 'intention-to-treat' basis, there were no significant differences between the experimental and control groups. However, when patients who practised at least daily were compared with those in the control group, the former were significantly less anxious ($F=6\cdot 34$, $P<0\cdot 02$) and less depressed ($F=4\cdot 86$, $P<0\cdot 04$). They also had fewer psychological symptoms as assessed by the RSCL ($F=4\cdot 36$, $P<0\cdot 04$) Within the experimental group, patients practising at least daily were less anxious ($F=11\cdot 44$, $P<0\cdot 002$), less depressed (time × subgroup interaction, $F=1\cdot 92$, $P<0\cdot 04$) and had fewer psychological symptoms ($F=4\cdot 76$, $P<0\cdot 04$). In contrast, an intention-to-treat analysis of global quality of life during chemotherapy showed that patients receiving the experimental intervention had better quality of life regardless of the frequency of practice (relaxation × time interaction, ($F=5\cdot 68$, $P<0\cdot 02$).

These data clearly indicate that this simple intervention is of considerable benefit to women willing to practice at least daily during chemotherapy. There are clear implications for management.

Matrix metalloproteinase expression in human breast tumours

E. A. Garbett, M. W. R. Reed and N. J. Brown, *Department of Surgical and Anaesthetic Sciences, University of Sheffield, Sheffield, UK*

Matrix metalloproteinases (MMPs) are a family of Ca^{2+} and Zn^{2+}-dependent enzymes that are responsible for the degradation of extracellular matrix (ECM) components in both physiological and pathophysiological processes. They are thought to have an important role in human tumour invasion and metastasis.

The aim was to compare the expression of latent and active forms of MMP for breast tumour ($n=40$), surrounding 'normal' breast ($n=33$) and the breast cell line MCF-7 ($n=10$) This was determined by zymography.

The substrate within the zymogram was altered depending on the MMP of interest: gelatin for the gelatinases (MMP-2 and MMP-9), casein for stromelysin 1 (MMP-3) and collagen I for the interstitial collagenase (MMP-1). Cell lysates (1×10^7 cells per ml lysis buffer) were run on an electrophoretic gel with a molecular weight marker.

The percentage of samples expressing latent and active forms of MMP were as shown in the *Table*.

Sample	Latent MMP-2 (72 kDa)	Active MMP-2 (66 kDa)	Latent MMP-9 (92 kDa)	Active MMP-9 (84 kDa)	Latent MMP-3 (57 kDa)	Active MMP-3 (28 kDa)	Latent MMP-1 (57 kDa)
Tumour	100	100*	93	58*	59*	22	79*
Normal	97	67	91	3	12	8	39
MCF-7	100	0	100	0	0	0	0

*$P < 0{\cdot}001$ *versus* normal (χ^2 test)

To establish that all the bands were due to MMPs, the gels were incubated with either ethylenediamine tetra-acetic acid (a calcium chelator) or 1,10-phenanthroline (a zinc chelator). All the bands disappeared.

All tissue expressed latent and active forms of MMPs. There was a significantly greater proportion of tumours expressing the active MMPs compared with background tissue. However, expression of MMPs in the breast tumour cell line did not correspond to that found in cancer or normal breast tissue, suggesting that the active MMPs came from stromal cells.

Positron emission tomography is useful in assessing axillary lymph nodes in breast cancer

K. N. Ogston, P. Whitford, P. Sharp*, F. Smith†, S. D. Heys and O. Eremin, *Departments of Surgery and *Biomedical Physics, University of Aberdeen and †Department of Nuclear Medicine, Aberdeen Royal Infirmary, Aberdeen, UK*

The single most important prognostic factor in breast cancer is axillary node involvement by tumour. Clinical assessment of axillary nodes is unreliable and the only method of establishing regional lymph node status is by surgical exploration (clearance or sample) However, axillary surgery is associated with significant postoperative morbidity and it would be valuable to have a non-invasive method of assessing axillary nodes. Positron emission tomography (PET) can image metabolic processes *in vivo* and, unlike other imaging modalities, may be able to distinguish between reactive nodes and nodes containing malignant cells. The aim of this study, therefore, was to assess the role of PET in staging the axilla in patients with breast cancer.

Twelve patients with breast cancer were evaluated. Following clinical examination of the axilla, PET imaging of the axillae and upper thorax was performed using a Siemens EXACT 31 scanner. The metabolic substrate used was [^{18}F]/fluoro-2-deoxy-D-glucose (FDG). At the time of mastectomy and surgical treatment of the axilla (sample or clearance), the axillary nodes were retrieved at operation, and carefully dissected and counted before undergoing histological examination. The accuracy of clinical examination and PET node staging was compared with node histology.

Twelve patients underwent PET imaging of the axilla before mastectomy and axillary node dissection. Five had positive axillary nodes at histology. PET was positive in all five cases; of these three had palpable nodes clinically. Seven patients had no involved nodes histologically. PET was positive in one and negative in six; four had palpable nodes.

Thus, PET had a specificity of 86 per cent and a sensitivity of 100 per cent; clinical examination had a specificity of 43 per cent and a sensitivity of 60 per cent.

In conclusion, PET imaging may have a role in staging the axilla in patients with breast cancer, thus avoiding unnecessary surgery.

Prospective validation of dynamic magnetic resonance mammography in the breast following cancer therapy

P. J. Drew, S. Mussurakis, L. W. Turnbull, D. Buckley, S. Bowsley, J. N. Fox, P. J. Carleton, A. Horsman and J. R. T. Monson, *University of Hull Academic Surgical Unit, Castle Hill Hospital and the Centre for Magnetic Resonance Investigations, Hull Royal Infirmary, Hull, UK*

The accurate clinical and mammographic detection of residual or locally recurrent disease following breast-conserving surgery, neoadjuvant therapy or prosthetic reconstruction is currently problematic. Dynamic contrast-enhanced magnetic resonance mammography (MRM) represents an alternative diagnostic modality.

A total of 102 patients were recruited. Therapy included wide local excision ($n = 89$), mastectomy and reconstruction ($n = 4$) and neoadjuvant radiotherapy or chemotherapy ($n = 9$). Primary histological diagnosis included invasive ductal cancer ($n = 81$), ductal carcinoma *in situ* ($n = 8$), invasive lobular cancer ($n = 8$), medullary cancer ($n = 2$), mucinous cancer ($n = 2$) and inflammatory breast cancer ($n = 1$). MRM was performed a median of 1·3 (interquartile range (i.q.r.) 1–3·1) years following surgery and a median of 1 (i.q.r. 0·6–2) years after adjuvant radiotherapy or chemotherapy. Patients have been followed clinically and mammographically for a median of 1 (i.q.r. 0·5–1·3) years following MRM.

In the neoadjuvant therapy group four cases (44 per cent) of residual disease were identified solely by MRM. Local recurrence following wide local excision was confirmed in five patients (6 per cent) during the period of the study. Positive predictive values for clinical, mammographic and MRM detection in this group were 0·29, 0·30 and 0·57 respectively.

Dynamic MRM is the most accurate imaging modality for the evaluation of residual or locally recurrent breast cancer. Clinical and mammographic investigations were associated with an unacceptably low specificity in these groups.

It is concluded that women at high risk of recurrent breast cancer or those with equivocal results from traditional investigations should be evaluated with dynamic MRM before any surgical intervention.

Angiogenesis in breast disease

M. W. R. Reed, R. M. Lindley and T. J. Stephenson, *Departments of Histopathology and Surgical and Anaesthetic Sciences, University of Sheffield, Sheffield, UK*

Several studies indicate increased microvessel counts (angiogenesis) in invasive breast cancer but little is known about vessel counts in benign and premalignant disease. The aim of this study was to investigate the relationship between angiogenesis and the transition from benign breast disease to atypical hyperplasia, and from carcinoma *in situ* (CIS) to microinvasive breast cancer. Von Willebrand-positive staining was used to identify blood vessels in three areas per section.

Type of lesion	No. of patients	Vessel count*
Fibrocystic change	11	58 (39–76)
Hyperplasia		
No atypia	8	53 (35–72)
Atypical	19	57 (46–67)
CIS	48	83 (72–94)†
Microinvasive carcinoma	5	95 (38–152)

*Values are mean (95 per cent confidence interval). †$P < 0{\cdot}05$ *versus* atypical hyperplasia (Kruskal–Wallis one-way analysis of variance)

There was a significant increase in microvessel density between atypical hyperplasia and CIS but not between CIS and microinvasive carcinoma. This indicates that the onset of angiogenesis may occur before the appearance of invasive carcinoma

Does tamoxifen increase bone resorption in premenopausal women?

N. J. Bundred, K. Naylor, J. Walls, G. Evans, R. Eastell and A. Howell, *Departments of Surgery and Cancer Research Campaign Medical Oncology, University Hospital ot South Manchester and Department of Clinical Biochemistry, University of Sheffield, UK*

Oestrogen is necessary for the maintenance of bone mass in premenopausal women and postmenopausally bone resorption increases, leading to osteoporosis. The antioestrogen tamoxifen is being tested in primary prevention trials as prophylaxis against breast cancer. Potentially it may antagonize oestrogenic bone formation in premenopausal women leading to increased bone breakdown

To determine the effect of tamoxifen on bone resorption, 40 women entered into the prevention trial provided urine at baseline before entry and at 6 months of treatment. Urinary free deoxypyridinoline and C-telopeptide of type I collagen (crosslaps), sensitive markers of bone resorption, were measured by means of commercial kit assays. In 19 postmenopausal women tamoxifen ($n = 12$) decreased urinary crosslaps compared with placebo ($n = 7$) ($z = 2{\cdot}54$, $P \leq 0{\cdot}02$). At 6 months urinary crosslaps fell significantly from the baseline level in tamoxifen- and placebo-treated premenopausal women ($P = 0{\cdot}003$ and $P \leq 0{\cdot}05$ respectively) but did not differ between groups

		Free deoxy-pyridinoline		Crosslaps	
Pre-menopausal	*n*	Baseline level*	Ratio (6 months/ baseline)†	Baseline level*	Ratio (6 months/ baseline)†
Tamoxifen	11	5·5(1·4)	0·75 (0·48–1·0)	159·3(59)	0·49 (0·22–1·0)
Placebo	10	4·8(0·8)	0·71 (0·50–1·3)	180·4(103)	0·43 (0·14–3·2)

Values are *mean(s.d.) and †mean (range). Wilcoxon rank analysis showed no differences between the groups

Tamoxifen acts as an oestrogen on postmenopausal bone and does not antagonize oestrogen in premenopausal bone. Its use in premenopausal women will not lead to increased osteoporosis.

Controlled trial of L-arginine and chemotherapy *versus* chemotherapy alone in patients with large or locally advanced breast cancer

K. Ogston, S. D. Heys, L. G. Walker, O. Eremin and the Aberdeen and Dundee Breast Group, *Departments of Surgery, Oncology, Radiology and Pathology, University of Aberdeen and Department of Surgery and Clinical Oncology, University of Dundee, UK*

Recent interest in the treatment of patients with large primary breast cancer has focused on the use of neoadjuvant chemotherapy. Previous studies have demonstrated that dietary supplementation with L-arginine (given for 3 days) could enhance the immune response and stimulate tumour metabolic activity This may enhance the susceptibility of the malignant cells to chemotherapy.

The aim of this double-blind placebo-controlled study, therefore, was to evaluate the effects of L-arginine in combination with chemotherapy in patients with large or locally advanced primary breast cancer.

Some 96 patients with large primary or locally advanced breast cancers (T$_2$, 30 patients; T$_3$, 52; T$_4$, 14) were entered into a phase III trial evaluating the efficacy of L-arginine in combination with chemotherapy Patients received six pulses of chemotherapy, comprising doxorubicin 50 mg m^{-2}, cyclophosphamide 1 g m^{-2}, vincristine 1·5 g m^{-2} and prednisolone 40 mg orally for 5 days, at 21-day intervals In addition, patients were randomized to receive dietary supplementation with L-arginine (30 g per day) or placebo for 3 days immediately before each cycle of chemotherapy.

The response rate (complete and partial) was 72 per cent in patients receiving L-arginine and chemotherapy *versus* 71 per cent in those having chemotherapy alone. Imaging modalities (mammography and ultrasonography) revealed no differences in response rate. All patients underwent surgery following chemotherapy (wide local excision or mastectomy) and histological evaluation of residual tumour was undertaken.

The complete pathological response rate was 18 per cent in patients receiving L-arginine and chemotherapy *versus* 11 per cent in those having chemotherapy alone (*P* not significant). Median survival and progression-free survival were comparable for the two groups of patients.

This study demonstrates that the addition of L-arginine to chemotherapy does not result in an increased response rate or prolongation of disease-free survival in patients with large or locally advanced breast cancer.

Differential oxidase and acetylase activity in human breast cancer: regulation of growth control

H. M. Wallace, J. Duthie, S. Lamond, D. M. Evans, O. Eremin and S. D. Heys, *Departments of Medicine and Therapeutics, Biomedical Sciences and Surgery, University of Aberdeen, Aberdeen, UK*

The polyamines are naturally occurring aliphatic amines found in all living cells They are essential for continuous cell growth and their intracellular concentration is raised in rapidly growing cells and tissues, and in cancer cells. For example, in breast cancer tissue a 3–4-fold increase in polyamine concentration is observed compared with that in normal breast tissue. In addition, increased amounts of monoacetylated polyamines are found in human tumour tissue. The increase in acetylated polyamines could result from increased activity of N^1-acetyltransferase (N^1-SAT), which produces these derivatives, or from a decrease in the level of polyamine oxidase (PAO), which catabolizes them. The aim of this study was to measure polyamine catabolic enzymes in normal and tumour tissue and to determine why acetylpolyamine content is increased in malignant tissue.

PAO and N^1-SAT activities were measured, using high-performance liquid chromatography, in normal and tumour tissue homogenates from patients undergoing surgery for breast carcinoma. PAO activity was decreased significantly ($P < 0{\cdot}005$, Wilcoxon signed rank test) in tumour tissue compared with normal tissue in all samples analysed ($n = 9$). The mean(s.e.m.) activity for normal and tumour tissue was 400(99) and 69·0(21·9) pmol per min per mg protein respectively. In contrast N^1-SAT activity was increased significantly ($P < 0{\cdot}001$) in tumour compared with normal tissue (10·8(4·3) *versus* 2·7(0·6) pmol per min per mg protein respectively).

Thus, the increased level of acetylated polyamines found in breast cancer tissue results from both increased synthesis and decreased catabolism of the acetyl derivatives. These enzymes represent novel targets for the manipulation of polyamine content of human tumours, and effectors of N^1-SAT and PAO may have potential use in the management of tumour growth.

Eicosapentaenoic acid, cytokines and the acute-phase protein response in pancreatic cancer

S. J. Wigmore, K. C. H. Fearon, J. A. Ross and D. C. Carter, *University Department of Surgery, The Royal Infirmary, Edinburgh, UK*

The acute-phase protein response (APPR) is raised in patients with pancreatic cancer cachexia and has been shown to correlate with increased energy expenditure and decreased survival duration. Production of proinflammatory cytokines by peripheral blood mononuclear cells (PBMCs) from patients with pancreatic cancer is significantly raised and has been implicated in the induction of the APPR. Previous work has demonstrated that n-3 polyunsaturated fatty acids downregulate cytokine production in healthy volunteers and eicosapentaenoic acid (EPA) has been shown to have anticachectic effects in humans.

This study examined the effect of dietary supplementation with high-purity EPA in patients with pancreatic cancer on PBMC cytokine production and acute-phase protein production *in vitro* and *in vivo*.

Six patients with irresectable pancreatic cancer received a total of 92 g 95 per cent pure EPA in the form of gelatin-coated capsules over 1 month. Serum C-reactive protein (CRP) concentration was measured before and after supplementation. PBMCs were isolated from these patients before and after supplementation, and also from six healthy volunteers. Spontaneous and lipopolysaccharide (LPS)-induced tumour necrosis factor (TNF) and interleukin (IL) 6 release were measured by enzyme-linked immunosorbent assay (ELISA). PBMC supernatants were also added to isolated human hepatocytes and acute-phase protein production was measured by ELISA.

Monoclonal anti-TNF and IL-6 antibody inhibited the potential of PBMC supernatants to stimulate an APPR by hepatocytes. EPA supplementation resulted in reduction of TNF and IL-6 production. Following EPA supplementation, production of CRP in response to PBMC supernatants from patients with cancer by isolated human hepatocytes was reduced and serum concentrations of CRP also fell significantly.

	Before supplementation		After supplementation	
	0	LPS (5 μg ml^{-1})	0	LPS (5 μg ml^{-1})
PBMC IL-6 (ng ml^{-1})	3·2(0·4)	10·2(0·9)	0·7(0·1)*	3·6(0·3)*
PBMC TNF (ng ml^{-1})	487(43)	1210(156)	199(24)	643(72)*
Hepatocyte CRP (ng ml^{-1})	107(7)	196(16)	89(6·2)	96(6·4)*
Serum CRP (mg l^{-1})	11·2(4·8)		0·83(0·8)*	

Values are mean(s.d.). *$P < 0{\cdot}05$ *versus* before supplementation (analysis of variance)

These data support clinical observations that the anticachectic effect of EPA in pancreatic cancer may be mediated through suppression of cytokine production and the hepatic acute-phase response.

Is expression of the human regenerating protein gene (*reg*) in colorectal cancer a predictor of poor survival?

R. C. A. Macadam, L F. Woodhouse, S. M. Farmery and P. J. Guillou, *Academic Unit of Surgery, St James's University Hospital, Leeds, UK*

Human *reg* messenger RNA (mRNA) has been detected in regenerating islet cells of the pancreas and is postulated to have a role in modulating cell replication, growth and maturation. This study examined the expression of this potential oncogene in tumour and mucosa samples from patients with colorectal cancer.

Tumour and adjacent mucosa samples were analysed from 32 patients who had undergone resectional surgery for colorectal cancer and for whom a minimum of 2 years' follow-up was available. RNA was extracted using a cationic surfactant method. A novel reverse transcriptase–polymerase chain reaction was performed using primers designed to amplify a 263-base-pair fragment of the *reg* gene, detected by agarose gel electrophoresis.

reg mRNA was strongly expressed in 20 tumours, whereas 12 expressed no detectable *reg* mRNA Expression of *reg* mRNA was detected in four mucosa samples adjacent to *reg*-expressing tumours. In contrast, no *reg* expression was detected in mucosa adjacent to *reg*-negative tumours. Patients with *reg*-expressing tumours showed a significantly increased incidence of cancer-specific death over the 2-year follow-up period.

	reg-positive tumours	*reg*-negative tumours
Cancer-specific deaths	11 of 20	1 of 12

$P < 0{\cdot}05$ (χ^2 test with Yates' correction)

These results demonstrate the ectopic expression of *reg* in a majority of colorectal carcinomas, and an association with poorer disease-specific survival Expression of *reg* in adjacent mucosa may be a feature of a field change in some cases of colorectal cancer.

Expression of CD44v6 in colorectal cancer: possible association with p53 mutation

M. Morrin. T. McCarthy and P. V. Delaney, *Colorectal Research Unit, Limerick Regional Hospital and University of Limerick, Ireland*

The glycoprotein CD44 is a cell adhesion molecule believed to play a role in normal lymphocyte migration and binding. By a mechanism known as alternative splicing, the CD44 gene can produce many variant messenger RNA transcripts. In neoplasia, many abnormal splice variants are produced. CD44 variant glycoproteins with sequences encoded by exon v6 confer full metastatic potential to rat carcinoma and sarcoma cell lines Overexpression of CD44 variant proteins has been observed to be related to the progression of colorectal cancer. This study investigated the expression of the variant CD44 encoding exon v6 (CD44v6) in normal and malignant colorectal tissue and whether this variant expression has any association with mutations in the p53 tumour suppressor gene.

Immunohistochemistry was used to detect CD44v6 expression in archival tumour specimens. Protein expression was confined to the cell membranes. No staining was seen in normal colorectal tissue. Some 78 tumour specimens were examined. A lower proportion of the non-metastatic Dukes A and B tumour specimens expressed CD44v6 (61 per cent) compared with metastatic Dukes C and 'D' tumours (72 per cent). In attempting to establish whether CD44v6 expression signifies poorer prognosis, 5-year survival data for the Dukes B group were examined. The CD44v6-positive group had a 50 per cent 5-year survival rate, whereas 65 per cent of patients who did not express this variant were alive 5 years later. Nearly 70 per cent of the Dukes B CD44v6-positive group was observed to have overexpression of the p53 protein, compared with 43 per cent of the CD44v6-negative group. Whether this association is a manifestation of the genetic disarray of the tumour cell or signifies a more profound involvement is unclear.

The anti-idiotypic monoclonal antibody 105AD7 increases lymphocyte infiltration within colorectal tumours

C. A. Maxwell-Armstrong, T. J. D. Buckley, L. G. Durrant, J. H. Scholefield and J. D. Hardcastle, *Department of Surgery, University Hospital, Nottingham, UK*

The anti-idiotypic monoclonal antibody 105AD7 has shown a 300 per cent survival advantage in patients with advanced colorectal cancer, with no associated toxicity. Evidence of helper T cell responses, enhanced autologous tumour cell cytotoxicity and increased natural killer (NK) activity has been induced in the peripheral circulation.

To assess whether similar immune responses can be seen at the tumour site, five patients with primary colorectal cancer were immunized before operation with a 10-μg intradermal injection of 105AD7 vaccine, followed by 50 μg intramuscularly 48 h later. A further patient received a second course. Sections were taken from normal bowel, two distinct tumour edges and the tumour centre. Immunohistochemical analysis was performed using monoclonal antibodies to CD4 (helper), CD8 (cytotoxic) and CD56 (NK cell) lymphocyte subsets. Tumours from an age- and sex-matched unimmunized group with identical tumour site, stage and differentiation were also stained.

Despite a wide variation in tumour infiltration, paired analysis showed a significant ($P = 0{\cdot}04$) increase in lymphocyte infiltration in tumours from immunized patients. Infiltration of tumour relative to normal bowel was also increased in patients receiving 105AD7 (mean 0·684 *versus* 1 438, $P = 0{\cdot}003$)

Immunization with 105AD7 increases lymphocyte accumulation at tumour sites.

Antitumour efficacy of taurine and recombinant interleukin 2 *in vivo*

N. M. Finnegan, H. P. Redmond, M. L. Da Costa and D. J. Bouchier-Hayes, *Department of Surgery, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland*

The administration of recombinant interleukin (rIL) 2 is limited by the induction of increased microvascular permeability causing the associated vascular leak syndrome. In this study the *in vivo* antineoplastic effects of the β-amino acid taurine in combination with rIL-2 were investigated and its impact on the associated vascular leak was examined. Lung metastases of B16 melanoma cells were established in mice via tail vein injection. Ten days after injection mice were randomized into four treatment groups: rIL-2, 50 000 units per 0·5 ml, taurine 5 mg per 0·5 ml, taurine plus rIL-2, and rIL-2 plus glycine. All treatments were given as intraperitoneal injections every 8 h for 5 days, with control animals receiving saline. On day 18 after tumour injection the mice were killed; lungs were removed and weighed, and metastases counted in a blinded fashion with the aid of a dissecting microscope; spleens were excised to obtain single cell suspensions and to establish splenocyte antitumour activity.

Treatment	No. of metastases
Control	155(24·0)
rIL-2 (50 000 units)	64(21·3)*
rIL-2 plus taurine (10 mmol l^{-1})	21(6·4)†‡
Taurine (10 mmol l^{-1})	111(32·8)
rIL-2 plus glycine	66(29·8)

Values are mean(s.e.m.). *$P = 0{\cdot}05$, †$P < 0{\cdot}001$ *versus* control; ‡$P < 0{\cdot}05$ *versus* rIL-2

Treatment of tumour-bearing C57BL/6 mice for 5 days with rIL-2 alone resulted in a significant reduction in tumour nodule incidence compared with that in a control group, while the group receiving rIL-2 plus taurine showed an even further reduction. To examine the effect of taurine on rIL-2-induced pulmonary oedema, wet and dry lung weights were assessed. Animals receiving rIL-2 showed a significant ($P < 0{\cdot}01$) increase in mean wet lung weight compared with control lung weight, while mean wet lung weight of the rIL-2 plus taurine group was significantly lower ($P < 0{\cdot}05$) than that of the rIL-2 group. Animals that received rIL-2 plus taurine *in vivo* demonstrated significantly enhanced ($P < 0{\cdot}05$ at effector to target ratio of 100 : 1 and 40 : 1) rIL-2-activated, splenocyte-mediated, antimelanoma activity *ex vivo* compared with those receiving rIL-2 alone.

Taurine may have an important role in modulating both the anticancer efficacy and the associated toxicity of rIL-2 immunotherapy and may permit dose escalation of this treatment.

Role of γ-linolenic acid in modulating the cytotoxicity of different chemotherapeutic agents on pancreatic carcinoma cell lines *in vitro*

A. H. Ben Younes, S. Richardson, S. D. Heys and O. Eremin, *Department of Surgery, University of Aberdeen Medical School, Aberdeen, UK*

The essential fatty acid γ-linolenic acid (GLA) can inhibit the proliferation of a variety of human cancer cell lines *in vitro*, and tumour growth *in vivo* (animal studies). Furthermore, polyunsaturated fatty acids (PUFAs) can alter the membrane composition and fluidity, thus influencing membrane permeability. This is relevant to many cytotoxic drugs, which are thought to enter the cell by passive diffusion.

A study was made of the effect of GLA in modulating the cytotoxicity of different chemotherapeutic agents (5-fluorouracil (5-FU), doxorubicin, cisplatin and mitomycin C) on two pancreatic carcinoma cell lines (Panc-1 and PaCa2). Cells were grown under standard conditions, harvested and seeded as 2–3 × 10^3 cells per well in 96-well plates. GLA was added 24 h later (to achieve final concentrations of 10, 20 and 30 μg ml^{-1}) and different concentrations of the chemotherapeutic agents (0·01–10 μg ml^{-1}) were added. Control wells contained medium, GLA or the cytotoxic agents only. Plates were kept at standard conditions and cell viability was assessed by a microculture tetrazolium (MTT) assay after 96 h of exposure. Each experimental procedure was done in quadruplicate and three sets of experiments were carried out.

Addition of GLA enhanced the cytotoxic effects of anticancer drugs. Isobologram analysis of the interaction between GLA and the cytotoxic agents was shown to be additive. This combination may have important clinical implications in the management of patients with cancer

	OD	
GLA (μg ml^{-1})	Doxorubicin (0·01 μg ml^{-1})	Mitomycin C (0·01 μg ml^{-1})
0	1·014(0·0395)	1·422(0·460)
10	0·8490(0·0255)*	0·831(0·0195)*
20	0·7020(0·0100)*	0·798(0·0235)*
30	0·5850(0·0165)*	0·674(0·0485)*

Values are mean(s.e.m.). OD, MTT optical density corresponding to viable cell number. *$P < 0{\cdot}001$ *versus* control (one-way analysis of variance, Bonferroni test)

Prolonged increase in tumour : normal blood flow ratio is achieved with continuous angiotensin II infusion in patients with colorectal liver metastases

D. Burke, M. Davies, J. Zweit*, H. Young*, M. Flower*, P. Carnochan*, R. J. Ott* and T. G. Allen-Mersh, *Department of Surgery, Charing Cross and Westminster Medical School and *Department of Physics, Institute of Cancer Research, London, UK*

Hepatic arterial infusion of the vasoconstrictor angiotensin II (AII) over 90 s has been shown to increase tumour blood flow and chemotherapy uptake but it is not known whether increased tumour blood flow can be sustained for longer. The development of blood flow tracer with a short half-life (^{62}Cu–PTSM, copper–pyruvaldehyde-*bis*-(*N*-4-methylthiosemicarbazone) now makes it possible to measure blood flow repeatedly over a longer period.

Tumour and liver blood flow was studied in eight patients with colorectal liver metastases who received a 45-min hepatic arterial AII infusion. Blood flow was determined before, during and at the end of this infusion by hepatic arterial administration of ^{62}Cu–PTSM, whose distribution was measured with a positron emission tomography scanner.

AII infusion	T:N ratio (^{62}Cu–PTSM counts)	Mean blood pressure (mmHg)
Before	1·35 (0·90–2·47)	97·5 (97–108)
During	1·95 (1·41–4·11)[*]	113·5 (109–115)[*]
At end	1·68 (1·31–3·81)[†]	100·5 (99–105)

Values are median (interquartile range). [*]$P<0{\cdot}02$ *versus* before infusion; [†]$P<0{\cdot}05$ *versus* during infusion (signed rank test)

There was an initial increase in the tumour:normal liver ratio which persisted throughout the 45-min AII infusion. An associated blood pressure rise returned to normal on cessation of AII infusion. This is the first demonstration that AII-induced enhancement of tumour:normal liver blood flow ratio can be sustained during prolonged AII infusion in patients with colorectal liver metastases

Expression of matrix metalloproteinases in colorectal adenoma and carcinoma

S. L. Parsons, H. M. Collins, P. A. Clarke, S. A. Watson and R. J. C. Steele, *Department of Surgery, University Hospital, Nottingham, UK*

Matrix metalloproteinases (MMPs) are a family of enzymes that degrade the extracellular matrix, a process that is essential for tumour invasion and metastasis. There is now convincing evidence that MMPs are overexpressed in many cancers, including colorectal cancer. Little is known about how early in the adenoma–carcinoma sequence the MMPs are expressed.

The aim of this study was to measure the expression of MMP-2 and MMP-9 in normal colorectal mucosa, benign adenoma and colorectal cancer, using the technique of gelatin zymography. Fifty-three colorectal cancers and corresponding normal mucosa were studied along with 15 colorectal adenomas.

	MMP-9	Inactive MMP-2	Active MMP-2
Normal	92·5 (0–2865)	43·7 (0–437)	0 (0–104)
Adenoma	673 (0–8060)	48 (0–199)	0 (0–24)
Carcinoma	1886·2 (72–12317)	92·1 (0–1253)	149·8 (0–4084)

Values are median (range) standard units

Adenomas overexpressed MMP-9 compared with normal mucosa ($P<0{\cdot}005$, Mann–Whitney U test), but expression of MMP-2 was unchanged in adenoma compared with normal mucosa. Colorectal carcinoma overexpressed MMP-9 and both forms of MMP-2 ($P<0{\cdot}0001$) compared with normal mucosa and adenoma ($P<0{\cdot}05$).

These findings provide further evidence that MMPs are important in colorectal cancer and suggest that MMP-9 (but not MMP-2) may have a role in the adenoma–carcinoma sequence.

Phase II trial of Marimastat (BB-2516) in advanced pancreatic cancer

J. D. Evans, S. R. Bramhall, A. Stark[*], H. Kinley[†], C. Porter[‡], L. Osborne[§], F. Daniel[‡], J. Carmichael[§], C. Imrie[*], C. D. Johnson[†] and J. P. Neoptolemos, *Queen Elizabeth Hospital, Birmingham, [*]Glasgow Royal Infirmary, [†]Plymouth General Hospital, [‡]Southampton General Hospital and [§]Nottingham City Hospital, UK*

Pancreatic cancer is characterized by aggressive local invasion and early metastasis and has been shown to produce large amounts of the matrix metalloproteinase (MMP) family of enzymes, but only low levels of their specific inhibitors (TIMPs). Marimastat (BB-2516) is a specific inhibitor (MMPI) of the MMPs and preclinical studies have demonstrated that MMPIs can restrict the growth and metastatic spread of solid tumours.

Some 50 patients (34 men and 16 women of median age 63 (range 35–82) years) with advanced pancreatic cancer were entered into a multicentre open phase II trial to assess the effect of 4 weeks' treatment with oral Marimastat (BB-2516), with the option for continued treatment in those with a clinical and/or radiological response. Some 27 patients (54 per cent) had liver metastasis at study entry. Nine initial patients were treated with 100 mg twice daily, while the remainder received 25 mg once daily.

Eight patients suffered musculoskeletal side-effects, which were most severe in those treated with 100 mg twice daily but mild in those treated with 25 mg once daily. There were no other significant adverse events. Serum levels of CA19-9 continued to rise steadily ($P<0{\cdot}05$, one-sample t test), whereas the C-reactive protein (CRP) level fell after 28 days (P not significant). Eleven of 22 assessable patients had progressive disease, with a median survival of 8 weeks; the other 11 patients, including six with stage IV disease, had stable disease assessed by computed tomography after 4 weeks, and all except one remain alive and well on treatment with a median survival of 13 weeks (median follow-up 14 weeks). The remaining patients included four who died early in the study and were not assessable and 24 who had not yet completed the trial. These preliminary data show promising results in some patients with pancreatic cancer but further studies are required to evaluate this novel treatment.

	Day 7	Day 14	Day 28	2 months
Change in CA 19-9 level (%)	3·3 (28)	21·7 (20)	51·1 (16)	93·6 (9)
Change in CRP level (%)	− 9·8 (20)	—	10 (14)	− 30 (6)

Values in parentheses are numbers at risk

British Journal of Surgery 1996, 83, 1653–1658

Correspondence

Conservative management of fibroadenoma of the breast

Sir

We read with interest the article by Dr Alle and colleagues (*Br J Surg* 1996; 83: 992–3) The paper raises the question as to whether conservative management of this condition is safe or indeed will be accepted by the majority of women if the facts are explained to them in a clear manner. It also questions the ideal frequency and duration of follow-up if the lesion is managed conservatively.

We raised concern over the diagnostic accuracy of clinical examination, mammography and fine-needle aspiration biopsy in young women presenting with a discrete breast lump in 1991[1]. This paper retrospectively reviewed a series of 2820 women presenting over a 19-year period with histologically proven breast cancer, 81 of whom were under the age of 36 years.

We agree that the most reliable single diagnostic investigation, particularly in this age group, is fine-needle aspiration cytology (FNAC). In our study the overall sensitivity was 78 per cent and no false-positive results were obtained. Clinical examination by a consultant was correct in 58 per cent of patients and mammography in only 45 per cent. During the study period, however, xeromammography was replaced by conventional mammography.

Interestingly, in ten (16 per cent) of 63 patients in whom all three modalities had been employed, all were falsely negative This led us to conclude that, where there was any doubt regarding the nature of the lesion, excision biopsy should be performed and that centres without combined mammographic and cytological facilities should proceed directly to excision biopsy without prior investigation. The operative approach, as well as having the advantages discussed by Dr Alle, also negates the need for 3-monthly follow-up[2].

Currently accepted protocols state that fibroadenomas over 4 cm in diameter should be excised. Conservative management is recommended in those under this size, where the patient is under the age of 40 years and assessment by clinical examination, ultrasonography and FNAC suggests fibroadenoma as the diagnosis, unless the patient requests excision[3]. In our experience this size is rarely attained; the mean size of tumours presenting in our study was 3 cm Our study also indicated that the upper age limit for conservative management of clinically benign discrete breast lesions would be better set at 25 years, as suggested by Cant *et al.*[4], because only four of the 81 patients with carcinoma were below this age.

We support the conclusions put forward by Dr Alle and his group and would strongly emphasize to any patient deciding on conservative management the possibility of false-negative triple assessment.

A. Yelland
J.-C. Gazet
R. C. Coombes

Department of Medical Oncology
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
UK

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An evaluation of the POSSUM surgical scoring system

Sir

We read with interest the paper by Whiteley and colleagues (*Br J Surg* 1996; 83: 812–15) We have also found POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) to overpredict mortality.

In the age of comparative audit and league tables of units and individual surgeons there is danger of inaccurate conclusions being reached as a result of misleading comparisons of crude mortality and morbidity data. This has been well illustrated in comparative audit in colorectal[1] and vascular[2] surgery. The importance of risk stratification as an audit tool to allow more meaningful comparisons is fundamental and has obvious implications in how results are presented. POSSUM has the advantages of being applicable across the specialties and easily derived from commonly measured factors. We have examined the accuracy of POSSUM in a single, purely vascular, practice.

Some 159 vascular operations under the care of a single vascular surgeon were studied and complications over a 30-day postoperative period recorded Estimated risk of morbidity and mortality was calculated by means of POSSUM logistic regression equations. Comparison of the estimated and observed rates of morbidity and mortality was performed with the χ^2 test to test the goodness of fit of the model The overall morbidity rate was 49 per cent with a mortality rate of 9·4 per cent. The estimated risk for morbidity from the POSSUM logistic regression equation did not differ significantly from the observed morbidity rates ($\chi^2 = 7{\cdot}8$, 9 d.f., $P > 0{\cdot}5$). Estimated mortality rates from the POSSUM equation, however, were significantly greater than observed rates ($\chi^2 = 13{\cdot}3$, 4 d.f., $P < 0{\cdot}01$). Using the Portsmouth predictor equation for mortality given in the Whiteley *et al.* paper (which uses the same physiological and operative scores as POSSUM), there was no significant difference between observed and predicted deaths ($\chi^2 = 4{\cdot}3$, 4 d.f., $P > 0{\cdot}5$).

The POSSUM scoring system predicts morbidity well but significantly overpredicts mortality. Adjustment with the Portsmouth predictor equation gives a significantly better fit between observed and predicted mortality.

M. J. Midwinter
S. Ashley

Directorate of Surgery
Level 7
Derriford Hospital
Plymouth PL6 8DH
UK

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Skin from the amputated limb should not be wasted

Sir

I was interested in the report by Mr Okoye and colleagues (*Br J Surg* 1996; 83: 797), which detailed four cases in which the skin of the amputated limb was used to graft contralateral ulcers. The authors gave no references, but as a matter of historical interest

I thought they may be interested to know that the first description of this technique is attributed to Sir Astley Paston Cooper of Guy's Hospital. Lord Brock's biography[1] details some 'short notes written in pencil at the end of his manuscript museum catalogues in the Royal College of Surgeons'.

> 'Copy of a curious and valuable paper.
> Hartfield, a young man admitted into Guy's Hospital (Cornelius ward) April 9th 1817, with a diseased thumb which Mr Cooper, now Sir Astley, amputated between the phalanges on the 18th July.
> He then cut off a healthy piece of integument from the amputated part and applied it to the piece of the stump where he secured it by means of adhesive slips.
> 1st week to July 25. Union seems to have taken place.
> 2nd week to August 1. Mr Cooper proved the vascularity of the newly attached portion by pricking it very slightly with the point of a lancet which produced blood as readily as from any other part of the limb Sensibility has not yet returned
> 3rd week from operation. In the course of this week sensation was restored in the end of the stump
> September 23rd. The stump appears quite well '

The present report coming 179 years later serves as a timely reminder both of the technique and of the old adage that 'there is nothing new under the sun'.

P. R. Taylor

Department of Surgery
Guy's Hospital
St Thomas Street
London SE1 9RT
UK

1 Brock RC. *The Life and Work of Astley Cooper.* Edinburgh: E & S Livingstone, 1952: 47–8.

Morphological classification of abdominal aortic aneurysm in selection of patients for endovascular grafting

Sir

The classification of aortic aneurysm morphology presented by Dr Schumacher and colleagues (*Br J Surg* 1996; 83: 949–50) is an interesting one, but the way in which the authors apply it to determining suitability for endovascular repair oversimplifies the issues and is potentially misleading In addition, a number of important details are omitted, making interpretation of their results difficult.

First, the size range of the aneurysms in the series is not stated – were small aneurysms included, and if so how many? Second, how did the authors define the proximal neck in types I–IIC? Both the width and length of the neck must be considered in the assessment of a patient's suitability for endovascular repair; this classification defines neither and may give the impression that width is not important. Third, most of the available bifurcated devices have very precise diameter ranges within which they can be used; no mention is made of dimensions within the broad categories of this classification. Fourth, it is not clear whether the authors consider type IIC aneurysms to be suitable for a bifurcated graft (as stated in one sentence) or not (as implied in their exclusion of this group from the overall calculations). We would concur with the latter position, as extending a bifurcated graft to below both common iliac bifurcations would exclude both internal iliacs, thereby compromising the pelvic circulation.

Crucially, the authors ignore the feasibility of using an aortouni-iliac endovascular graft in combination with a femorofemoral crossover graft. With this device, type IIC aneurysms become potential candidates for endovascular repair, as do an appreciable proportion of the patients considered unsuitable by the authors because of iliac occlusive disease or tortuosity. In our experience of 154 patients assessed for suitability for endovascular repair, 55 per cent were found to be suitable for this device and much smaller proportions than those found in this paper were suitable for either straight or bifurcated grafts[1].

M. P. Armon
S. W. Yusuf
B. R. Hopkinson

Department of Vascular and Endovascular Surgery
University Hospital
Nottingham NG7 2UH
UK

1 Armon MP, Yusuf SW, Latief K *et al.* The anatomical suitability of abdominal aortic aneurysms for endovascular repair. *Br J Surg* (in press).

Author's reply

Sir

Our reported prospective analysis (205 consecutive patients in a 3-year study period (1993–1995)) focused on the morphological classification and the precise data set of aortic dimensions as a basis for patient selection for endovascular grafting and correlation with the custom-made endograft size and shape before the procedure. *Table 1* summarizes the morphometric abdominal aortic aneurysm (AAA) data. The smallest AAAs are found in type I, and represent the best (and easiest) indication for endovascular grafting. These patients are not currently candidates for conventional AAA surgery.

Table 1 Aortic morphometry in 205 patients

		Type II			
Variable	Type I	A	B	C	Type III
No. of patients*	23 (11·2)	55 (26·8)	31 (15·1)	65 (31·7)	31 (15·1)
Aortic†					
Suprarenal	24 (22–26)	24 (19–28)	25 (20–28)	26 (23–30)	29 (26–31)
Infrarenal	22 (18–24)	22 (18–25)	22 (18–25)	25 (20–31)	33 (26–44)
Aneurysm	48 (38–56)	54 (45–62)	58 (48–85)	64 (45–110)	64 (53–77)
Bifurcation	22 (18–24)	24 (18–38)	28 (24–40)	45 (28–85)	33 (24–54)
Iliac†	13 (8–14)	13 (8–15)	16 (10–17)	34 (20–55)	22 (12–48)
Length (mm)†					
Proximal neck	26 (23–32)	23 (18–48)	22 (18–32)	18 (15–45)	5 (0–10)
Aneurysm	58 (38–67)	69 (40–110)	77 (60–110)	110 (80–140)	110 (75–140)
Distal cuff	22 (18–27)	—	—	—	5 (0–15)

*Values in parentheses are percentages; †values are mean (range)

Our definition of the proximal neck is that segment of non-dilated, thrombus-free, infrarenal aorta. Currently a proximal neck of at least 15 mm in length is required for safe and secure proximal stent–graft anchoring. With this definition in mind, the measured width is not important and differs considerably within the population. Endovascular grafting systems have been tested clinically and offer a broad spectrum of available maximum size and configuration. It depends on the endovascular system in use in the assessment of a patient's suitability for endografting.

We do consider type IIC aneurysms unsuitable for endografting because of the exclusion risk for both internal iliacs. We strictly reject the use of an aortouni-iliac endovascular graft in combination with a femorofemoral crossover graft for type IIC AAAs, because it is not possible safely to exclude the common iliac aneurysm left *in situ.* There could be a high risk for aneurysm rupture due to backbleeding and further expansion. In our experience of 205 patients, 53·1 per cent were suitable for endografting exclusively on morphology (types I, IIA and IIB), but only 30·3 per cent were good candidates, because of vascular co-morbidities.

H. Schumacher

Department of Surgery
Section of Vascular Surgery
Ruprecht-Karls University of Heidelberg
D-69120 Heidelberg
Germany

Use of glyceryl trinitrate ointment in the treatment of anal fissure

Sir

We read with interest the report by Mr Lund and colleagues (*Br J Surg* 1996; 83: 776–7). However, we consider that the authors have failed to address certain points.

The natural history of chronic anal fissure is such that some of the treated patients may have healed during the assessment[1,2] without administration of glyceryl trinitrate (GTN), and a group of placebo-treated patients would have controlled for this possibility. The short-term reversible effects of the chemical sphincterotomy described may result in an increased rate of recurrence of fissure after GTN therapy is stopped; hence reports of longer follow-up of the study would be of interest.

The use of only six 'normal' volunteers as controls to assess the concentration of GTN ointment seems weak. A larger control group should have been used or, more simply, the acceptance of previous work[3] quoted would have been more appropriate.

The dose of 0·5 g cannot be specific; while this dose may be 'typical', it should be stressed that dosage is approximate[4]. The authors fail to explain their rationale for a twice-daily dosage regimen. Although we acknowledge many reports of GTN used in this regimen, a recent report has suggested that more frequent dosage may be pharmacologically correct[4].

Finally, the main advantage of topical GTN would seem to be the relief of perianal pain due to anal sphincter spasm, without surgical sphincterotomy. Would it not, therefore, be of more benefit to use GTN as an analgesic for acute perianal conditions such as acute fissure, as reported by Gorphine[5], and following minor perianal operation when permanent sphincterotomy is not indicated?

D. P. Edwards
E. M. Chisholm

Department of Surgery
St Peter's Hospital
Chertsey KT16 0PZ
UK

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Authors' reply

Sir

We thank you for the opportunity to reply to the comments of Messrs Edwards and Chisholm. We agree that many acute fissures and a small proportion of chronic anal fissures may heal spontaneously. Most chronic fissures do not heal spontaneously, and patients will continue to be troubled by pain and bleeding on defaecation while waiting for sphincterotomy to be performed[1]. The median duration of symptoms at over 2 years suggests that patients in our study had already suffered quite prolonged trials of conservative management in the community. As there is growing concern over the incidence of continence impairment in those undergoing sphincterotomy, it seems sensible to look for non-surgical alternatives. A placebo-controlled trial is required for the development of this treatment, and we are sure that Messrs Edwards and Chisholm would agree that for the proper design of such a trial it is necessary to perform a small pilot study, as we have done. It may be that on longer follow-up a proportion of fissures treated with topical glyceryl trinitrate (GTN) will recur, but these recurrences may be successfully treated with a further course of nitrates.

As no reliable assay for GTN is available, it was necessary to perform a small clinical study to assess the dose regimen. The concentration used in the main study was the highest that did not produce severe headache. A twice-daily dosage regimen was chosen as it has previously been suggested[2] that topical GTN may reduce resting anal pressure for up to 9 h. A nitrate-free window is said to be desirable to avoid the development of tachyphylaxis.

Topical nitrates are of value in the treatment of acutely painful perianal conditions. As 18 of 21 chronic fissures in this study healed after 6 weeks' treatment, we suggest that topical GTN may be an effective treatment for chronic fissure.

J. Lund
J. Scholefield

Department of Surgery
Floor E, West Block
University Hospital
Queen's Medical Centre
Nottingham NG7 2UH
UK

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Severe complications of perianal sepsis in patients with human immunodeficiency virus

Sir

Dr Consten and colleagues (*Br J Surg* 1996; 83: 778–80) have highlighted that perianal sepsis should be suspected as a possible primary focus of infection in human immunodeficiency virus (HIV)-infected patients with abscesses in uncommon locations. It would be interesting to learn whether any of these patients, especially the one with a mediastinal abscess (possibly due to an infected lymph node), was detected as suffering from coexistent pulmonary or anorectal tuberculosis, for the following reasons. (1) There has been a recent resurgence of tuberculosis in the Western world and this closely parallels the rising association of *Mycobacterium tuberculosis* and HIV infection[1]. (2) Perianal tuberculosis has protean manifestations[2,3], including multiple perianal fistulas and abscesses similar to those described by the authors. (3) Finally, from an epidemiological point of view, infection with *M. tuberculosis*, when diagnosed definitively regardless of the presence of other causes of immune deficiency and in the presence of laboratory evidence of HIV infection, is an indicator disease for acquired immune deficiency syndrome[4].

A. I. Sarela

Department of Surgery
Royal Postgraduate Medical School
Hammersmith Hospital
Du Cane Road
London W12 0UD
UK

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Authors' reply

Sir

We are grateful for Mr Sarela's interest our article and for the opportunity to make some brief comments in reply. As to whether any of the patients with human immunodeficiency virus (HIV) infection with metastatic abscesses and a primary perianal focus were possibly also suffering from coexistent pulmonary or anorectal tuberculosis, the following answer can be given. Because the clinical presentation of these patients was quite rare in combination with their HIV status, all possible cultures and histopathological examinations were performed. Obviously, these tests included screening for infection with *Mycobacterium tuberculosis*, which was negative in all cases.

Although Mr Sarela is right that these manifestations might also be due to underlying *M. tuberculosis* infection, this was not the case in our patients.

E. C. J. Consten
F. J. M. Slors
H. Obertop
J. J. B. van Lanschot

Department of Surgery
Academic Medical Centre
Meibergdreef 9
1105 AZ Amsterdam
The Netherlands

A better bridge for loop stomas

Sir

Following the paper by Messrs Cochrane, Hay and Francis Jones (*Br J Surg* 1996; 83: 365), several letters have appeared in the correspondence column (*Br J Surg* 1996; 83: 1011, 1161). Can I be so bold as to suggest that, although important, the material used as a bridge for loop stomas is not the most critical part of the procedure? The factor that stops a good seal being produced is that the bridge comes out adjacent to the stoma and therefore the stoma bag has to be applied over it. This need can be avoided by making a small cut approximately 2 cm away from the lateral edge of the stoma on each side of it and burrowing subcutaneously to bring the bridge out there. This manoeuvre allows the stoma bag to be applied to ordinary skin and helps produce a better seal.

R. G. Wilson

Department of Surgery
South Cleveland Hospital
Marton Road
Middlesborough TS4 3BW
UK

Aspiring surgeons and temporary lecturer posts in anatomy

Sir

In recent years a junior doctor who hoped to become a surgeon was often advised to undertake a post as demonstrator or temporary lecturer in anatomy (TLA). Previous work[1] has confirmed that the holders of these posts achieved substantial success in their postgraduate diploma examinations and that the posts were highly thought of by former TLAs. However, there is a dearth of literature concerning the career achievements of such former demonstrators.

Data have recently become available from a postal questionnaire completed by former TLAs employed at the University of Manchester over a period of 16 years before 1991 (*Table 1*).

Table 1 Career achievements of former temporary lecturers in anatomy

TLA post	Men	Women	Total	Career decision
Anatomy only	73	3	76 (62)	55
Anatomy and accident and emergency	17	3	20 (16)	12
Anatomy and ophthalmology	17	5	22 (18)	16
Anatomy and RMO	4	1	5 (4)	2
Total	111	12	123 (100)	85

Values in parentheses are percentages. TLA, temporary lecturer in anatomy; RMO, Residual Medical Officer

The demonstrators undertook whole-time posts of anatomy only (for 9 months) or anatomy (for 3 or 6 months) paired with a clinical discipline (for 6 months). Manchester graduates represented 55 per cent of the doctors. Analysis of the 123 replies (from 12 women and 111 men) revealed that 73 per cent of 85 respondents holding career posts were employed in surgical specialties, 6 per cent in non-surgical hospital specialties, and 15 per cent worked in general practice. Surgical specialties represented included general surgery (15), ophthalmology (17), orthopaedic surgery (seven), accident and emergency (six), ear, nose and throat (five), and small numbers of practitioners in other surgical disciplines. Although the number of women is small, it is interesting to note that four of the eight holding career posts are ophthalmologists. The mean length of time from graduation to career appointment was 12 years for surgical specialties and 8 years for non-surgical careers.

At appointment most demonstrators are high achievers (50 of 123 held intercalated bachelor of science degrees) and highly motivated towards a career in surgery. That 6 per cent hold non-clinical career appointments is probably an indication of significant disenchantment with surgical training or medical practice generally in the UK. A few former TLAs commented on this issue, although it was not addressed specifically in our questionnaire.

Many readers will know that the future for university-funded demonstrator posts in anatomy is very uncertain in the current environment. As university funds have been squeezed, universities have been tempted to appoint 'researchers' who may improve departmental research profiles, and the number of part-time demonstrator posts funded through links with private hospitals has increased to a high proportion[2]. The undergraduate medical courses currently being promoted by the General Medical Council contain less anatomical information and, therefore, may be less useful to surgical trainees[3]. In addition, as anticipated by Miller and Neal[2] in 1994, changes in the regulations for surgical training seem to have made demonstrator posts less attractive to surgical trainees.

Nevertheless, it is clear that the intimate contact with anatomical material provided by the posts has been much appreciated by demonstrators, most of whom have progressed to surgical careers We hope that a suitable mechanism may evolve that will allow the traditional mutually beneficial relationship between undergraduate medical studies and surgical training to continue

P. Willan
I. Whitmore*
J. Humpherson†

Department of Human Anatomy
United Arab Emirates University
United Arab Emirates
and
**Department of Anatomy*
Queen Mary and Westfield College
London
†School of Biological Sciences
University of Manchester
Manchester M13 9PT
UK

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Blood flow in the lower limb after balloon angioplasty of the superficial femoral artery

Sir

I read with interest the article by Mr Hussain *et al.* (*Br J Surg* 1996; 83· 791–5) and I compliment them on their elegant method for assessing the relative flow in the profunda and superficial femoral arteries (SFAs) However, I believe that the method for calculating the collateral flow (Q_{Col}) is fundamentally flawed for at least two reasons.

First, the SFA flow resistance is assumed to be equivalent to that of an electrical resistor (R) where the relationship between the pressure drop (ΔP, mmHg) and the mean volume flow (Q, ml min^{-1}) is linear ($\Delta P = RQ$), i.e. R is assumed to be a constant with units of mmHg ml^{-1} min (or peripheral resistance unit (PRU)). Unfortunately, although this assumption is often made in the surgical literature, it is incorrect. Significant occlusive arterial disease creates disordered flow and the relationship between ΔP and Q becomes non-linear ($\Delta P = k_1Q + k_2Q^2$), where k_1 and k_2 are constants related to the geometry of the stenosis and the physical properties of the blood. This non-linear equation was suggested by Winsor[1] and later by May *et al.*[2], and confirmed experimentally by Young and Tsai for both steady[3] and pulsatile[4] flow. Indeed, for critical stenosis (area reduction of more than 75 per cent) the non-linear term becomes dominant[5] and a more accurate approximation is $\Delta P = k_2Q^2$, where k_2 is measured in mPRU ml^{-1} min (1000 mPRU = 1 PRU).

Second, the assumptions that (a) arterial and venous systems are coupled by a linear pressure–flow relationship (i.e. tissue resistance) and (b) venous pressure is zero when the patient is in the supine position are not consistent with experimental evidence. Physiologists have known for a long time that the pressure–flow relationship of the microcirculation is non-linear[6,7], with an apparent critical closure pressure (P_{cc}) of 20–30 mmHg that is believed to be due to (1) the collapsible nature of capillaries and (2) non-newtonian behaviour of blood in such small vessels.

To correct the electrical model for these non-linear effects, the SFA resistance should be replaced with the relationship $R_{SFA} = k_2Q_{SFA}$ and the mean venous pressure (V_{MVP}) should be set to around 25 mmHg. The resulting set of equations are non-linear and require a more complex method for their solution. However, this more sophisticated model predicts that, with significant SFA disease, flow to the calf or foot can become zero, a phenomenon that has been demonstrated *in vivo*[8] but which could not happen in the authors' simple linear model.

In making informed decisions about treatment based on clinical measurements it is necessary to have both accurate measurements and an accurate model for their interpretation. Linear electrical analogue models have often been used to represent the diseased arterial tree but there is neither the theoretical nor experimental evidence to support their continued use.

S. R. Dodds

Royal Hampshire County Hospital
Winchester SO22 5DG
UK

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Authors' reply

Sir

We appreciate the opportunity of responding to Mr Dodds' letter. It is important to point out that the main burden of our paper concerns the measurement of volume flow in the femoral vessels before and after angioplasty of the superficial femoral artery (SFA) The key observation was that the overall flow in the common femoral artery (both before and after exercise) does not change after angioplasty There is an increase in SFA flow with a concomitant reduction of flow in the profunda femoris artery (PFA). It therefore follows that flow in the PFA collaterals must have declined.

The possibility of assessing collateral flow by the use of a model of electrical resistance was originally suggested by Strandness and Sumner[1]. At a given point in time with the patient at rest we would still contend that peripheral resistance is constant. Therefore, although an offset to account for venous pressure may be required, the basic findings from the model remain valid. After exercise there is no doubt that the peripheral resistance will be changing rapidly and we would accept Mr Dodds' point that a series of non-linear equations would be required to provide an accurate measurement of collateral flow.

Mr Dodds rightly points out that accurate data are required if clinical decisions are to be made on the basis of non-invasive measurements. However, at no point in our paper do we suggest that a measure of collateral flow based on the electrical model should be used to determine the appropriateness or otherwise of any interventional procedure.

S. T. Hussain
R. F. M. Wood

Department of General Surgery
Norfolk and Norwich Health Care NHS Trust
Brunswick Road
Norwich NR1 3SR
UK

1 Strandness DE Jr, Sumner DS. Blood flow to the limbs. In: *Haemodynamics for Surgeons.* New York: Grunne Stratton, 1975: 209–89.

Routine preoperative infusion cholangiography at elective cholecystectomy: a prospective study in 694 patients

Sir
I am a little confused by the calculations in the recent article by Mr Hammarstrom *et al.* (*Br J Surg* 1996; 83: 750–4). In their study 625 patients had adequate opacification of the bile ducts at preoperative infusion cholangiography (PIC), of which 499 were normal and 128 abnormal, which leaves two unaccounted for. The authors claim a negative predictive value of 100 per cent for PIC based on a false negativity rate of zero, but there was a reference for the presence or absence of stones (in the form of operative cholangiography or endoscopic retrograde cholangiopancreatography (ERCP)) in only 44 of the 499 normal preoperative cholangiograms. We therefore have to assume that the remaining 455 preoperative cholangiograms were 'true negatives'. In any case, a positive predictive value of 94 per cent in this study for prominent common bile duct stones does make PIC an attractive investigation before ERCP or laparoscopic cholecystectomy for patients at high risk of common duct stones.

S. Sudhindran

Leighton Hospital
Crewe CR1 4QJ
UK

Author's reply

Sir
With regard to the value of 499, an unfortunate error was made and it should have been 497.

Of course, one cannot know for certain that no bile duct stones were overlooked by preoperative infusion cholangiography in the remaining 453 patients, but the negative predictive value (NPV) seems to be very high. Thus, we chose to express this slight uncertainty by 'can be regarded as evidence for', but we could just as well have used the phrase 'can be assumed to represent' instead.

The contrast density yielded by the infusion technique seems to be adequate and gives a high NPV. There are drawbacks to a low contrast density associated with intravenous cholangiography (IVC) and peroperative cholangiography which, unlike IVC, owes its low sensitivity to a high contrast density, especially in cases of dilated bile ducts.

L.-E. Hammarström

Department of Surgery
Lund University Hospital
S-221 85 Lund
Sweden

British Journal of Surgery 1996, 83, 1659–1661

Book reviews

Renal Vascular Disease

A. Novick, J. Scoble and G. Hamilton (eds). 260 × 192 mm. Pp. 539. Illustrated. 1995. London: W. B. Saunders. £75.

Our perception of renal arterial disease is like a view of an iceberg. Glimpses come our way, but there is a great deal more that we do not see. For example, we encounter a renal artery stenosis on an arteriogram and debate whether it should be bypassed, dilated, stented, or left untreated. A physician discovers a shrunken kidney in a difficult hypertensive and wonders whether it should be removed. A nephrologist demonstrates narrowed renal arteries in a patient approaching end-stage renal failure and considers revascularization as a last-ditch effort to keep dialysis at bay. The editors' chapters are on the progressive nature of atherosclerotic renal artery stenosis (J. Scoble), extra-anatomical renal revascularization of ischaemic nephropathy (A. Novick), and fibrinolytic therapy and secondary revascularization (G. Hamilton). The international cast of contributors includes Richard Dean on screening by duplex renal sonography and Sven-Eric Bergentz on renal artery endarterectomy. This comprehensive volume has illustrations of new magnetic resonance and spiral computed tomography angiography, and advice on such rarities as renal aneurysm and Takayasu's arteritis. However, we do not yet see all of the iceberg and a full-scale therapeutic assault on renal arterial disease remains around the corner. For the time being, interventions continue to be highly selected. The insights provided by this book help in the difficult choices faced on behalf of renovascular patients.

R. N. Baird

Bristol Royal Infirmary
Bristol BS2 8HW
UK

Applied Physiology for Surgery and Critical Care

M. A. Glasby and C. L.-H. Huang (eds). 281 × 221 mm. Pp. 756. Illustrated. 1995. Oxford: Butterworth-Heinemann. £95.

This is a multiauthor textbook describing applied physiology in relation to the practice of surgery; many chapters have been written by a single author, a senior lecturer in physiology. Not only is the content relevant and comprehensive, but it is written in a clear style which should be readily accessible to the reader. The page layout and excellent diagrams lend a lucidity to the work; in particular, the diagram explaining the changes in blood gases on page 302 is an asset to that particular chapter. Almost the whole of physiology is covered, including that of reproduction, development and growth, which is unusual in a surgical textbook (this book is also aimed at practitioners of critical care). At a time when the teaching of basic sciences for surgical trainees is changing with the introduction of the new MRCS exam, and there is an increasing requirement for young surgeons to be conversant with critical care issues, this book is a timely addition to the bibliography in this field. The authors, in their preface, confirm that the volume is aimed at the MRCS market, and it should become a standard text as the exam develops.

F. W. Cross

Royal London Hospital
Whitechapel
London E1 1BB
UK

Atlas of Laparoscopic Surgery

T. N. Pappas, L. B. Schwartz and S. Eubanks (eds). 312 × 254 mm. Pp. 300. Illustrated. 1995. Philadelphia, Pennsylvania: Current Medicine. £95.

This book is presented as an atlas of laparoscopic and thoracoscopic surgery aimed at the general surgeon. It therefore enters a crowded marketplace which is already well served with manuals of laparoscopic surgery. The book is multiauthor, but each chapter is handled in a standard format with a rather lengthy and unnecessary description of the history of the condition, followed by a brief description of anatomy, physiology and diagnosis, before schematic diagrams demonstrating the techniques themselves. The first chapter covers basic laparoscopy; I was surprised that scant attention has been paid to the general complications of laparoscopy itself. Subsequent chapters deal mainly with abdominal procedures, although some thoracoscopic and gynaecological ones are also included. In these chapters there are some rather obvious omissions· space precludes detailing them all, but the most notable one is the Watson operation for gastro-oesophageal reflux. The subsequent chapter on management of peptic ulceration covers the established laparoscopic techniques well, but does not see fit to include mention of *Helicobacter pylori* or, indeed, Billroth in the table detailing the major events in the history of peptic ulcer disease. Given that the text is aimed at general surgeons, it is good to see that a large proportion of the book is devoted to laparoscopic biliary surgery. Most surgeons would benefit from reading the chapter on complications of laparoscopic cholecystectomy and how to avoid them; this is, perhaps, the best part of the book. The chapter on laparoscopic colorectal surgery is disappointing. Of particular mention are the rather sketchy illustrations demonstrating an abdominoperineal resection for cancer; no self-respecting practitioner of total mesorectal excision would perform the operation illustrated here. Perhaps the most serious deficiency is the complete lack of detail with regard to the authors' personal experience with the operations they describe. While this volume may be of passing interest as a reference work in a departmental library, I cannot recommend that the individual rushes out to buy it as there are better alternatives already available.

R. G. Wilson

Western General Hospital
Crewe Road
Edinburgh EH4 2XU
UK

Cirugía. Fundamentos, Indicaciones y Opciones Téchnicas. 2nd ed. (3 volumes)

C. Pera. All volumes: 270 × 215 mm. Pp. 2652. Illustrated. 1996. Barcelona: Masson, S. A. Price unavailable.

This textbook is quite unique, in that all the basic aspects of general surgery, thoracic surgery, cardiovascular surgery, urology, trauma, orthopaedics and paediatric surgery are handled by a single author. One might expect that this could weaken the objective of providing the medical student with an update and depth of information. However, I found this book very interesting, well written and well illustrated, with clear text and easily understandable sketches and diagrams on facing pages. The most basic technical descriptions are presented in a precise, comprehensive and compact style that makes reading easy and pleasant. Writing a comprehensive book of this nature is difficult but the author has succeeded in producing a well balanced three volumes. I can recommend this as a valuable resource in a surgical department library, and to medical students and junior trainees in surgery.

L. Fernandez-Cruz

Hospital Clinic
Villaroel 170
08036 Barcelona
Spain

Diseases of the Breast

J. R. Harris, M. E. Lippman, M. Morrow and S. Hellman (eds). 285 × 225 mm. Pp. 1047. Illustrated. 1996. Philadelphia, Pennsylvania: Lippincott-Raven. £118.

This book is the current definitive work on diseases of the breast. Despite having only four European contributors, the authors have referenced key European papers, and so the book does not represent merely the American view of the subject. There are useful chapters on molecular epidemiology and the section on 'basic tools for advancing knowledge in breast cancer' including 'techniques in molecular biology and an interpretation of clinical trials' will prove useful to many struggling with these subjects. Malignant disease is dealt with more comprehensively than benign disease. In particular, old-fashioned advice is given on drainage of breast abscesses (repeat aspirations are infinitely preferable to incision and drainage). The illustrations are well chosen and well reproduced. Unfortunately, the cost has prevented colour, which is a shame as some illustrations would undoubtedly stand out better. This book should be readily available to all those who treat patients with breast cancer and both the established surgeon as well as the surgical trainee will find something in it for them.

J. R. C. Sainsbury

Royal Infirmary
Huddersfield HD3 3EA
UK

Cancer Surgery

J. C. Harvey and E. J. Beattie (eds). 289 × 220 mm. Pp. 599. Illustrated. 1996. Philadelphia, Pennsylvania: W. B. Saunders. £85.

This is a textbook that covers the surgery of all cancers in the body with the exception of those of the central nervous system. Each section is a multiauthored chapter covering a particular malignancy. They are authorative, well written and contain information that represents the state of the art. The editors have made an effort to ensure that there is a single style running through each chapter and they have been largely successful in this endeavour. Each chapter is liberally illustrated by diagrams, drawings and charts, making the points visually as well as in words. The illustrations are of a high standard. I found most of the book easy to read and learned some new things about types of cancer that I do not treat.

But who will read this book? The editors feel that it will be a valuable source book, not only for surgeons who have not made cancer their specialty but also for surgeons who are cancer specialists wishing to refresh themselves in certain areas. They also hope that it will be useful as a surgical text for medical and radiation oncologists, who want to find out what the surgeon does when he is treating cancer. I am not entirely sure about some of this; if I wished to refresh my understanding I think I would go to the library and obtain a specialist text, or read some of the modern review articles. Is there enough here to satisfy the medical or radiation oncologist? Despite this, I believe that this book will be valuable to the non-cancer specialist, and also to surgical trainees who want an overview of a particular subject or of the whole of cancer surgery. I will recommend it to our trainees.

G. W. Odling-Smee

Queen's University of Belfast
Institute of Clinical Science
Grosvenor Road
Belfast BT12 6BJ
UK

Principles of Endosurgery

K. R. Loughlin and D. C. Brooks (eds). 278 × 215 mm. Pp. 255. Illustrated. 1996. Oxford: Blackwell Science. £35.

Principles of Endosurgery suffers, like many books on endosurgery being produced these days, being passé before appearing in print. The objectives of this text are not clear, there being a mixture of some very general chapters and some highly detailed ones. The preface suggests that it was written for medical students and house officers, as well as consultants. Clearly the educational objectives of these groups are all different and cannot hope to be addressed in a book such as this. Of the 20 chapters, seven are dedicated to urology and will not have much appeal to the average endoscopic surgeon. Only six chapters deal with general surgical topics, while the rest deal with some basic issues. There is no mention of the problems of tumour seeding or capacitance coupling. Labelling of diagrams in some areas is not consistent. Although laparoscopic surgery is of topical interest, I think there are many better books on the market whose authors have succeeded better in what they have set out to do.

J. N. Baxter

Morriston Hospital National Health Service Trust
Morriston
Swansea SA6 6NL
UK

Warm Heart Surgery

T. A. Salerno (ed.). 257 × 193 mm. Pp. 230. Illustrated. 1995. London: Arnold. £85.

Techniques of myocardial protection are influenced by training, experience and reading. Wide variations exist between cardiac surgeons in the detail of their technique. However, until recently there was a general consensus that hypothermia was fundamental. With the 1991 reports of successful continuous warm blood myocardial protection by Salerno and colleagues from Toronto, this consensus has been challenged. There is currently great worldwide interest in warm heart surgery.

This book is highly topical. It places in one volume opinions from the leading authorities in the field. Divided into 26 chapters, this multiauthored text is comprehensive and fully referenced. A historical review of myocardial protection places warm blood cardioplegia in context. The authors have been successful in giving a clear and updated comprehensive account of what is a rapidly changing field and indicate future perspectives. While clearly advocating continuous warm blood cardioplegia, Dr Salerno acknowledges the efficacy of other techniques. Dr Buckberg's contribution is particularly valuable in achieving a balanced perspective. This is a valuable contribution to the literature and should be of interest to all surgeons, perfusionists and anaesthetists involved in open heart surgery.

P. D. Ridley

Bristol Royal Infirmary
Bristol BS2 8HW
UK

Arterial Conduits in Myocardial Revascularization

G. D. Angelini, A. J. Bryan and R. Dion (eds).
257 × 193 mm. Pp. 186. Illustrated. 1995. London: Arnold, £70.

Gianni Angelini and Alan Bryan have a well known and longstanding interest in conduits and myocardial revascularization. In this book they have collaborated with Robert Dion of Brussels to compile in one volume a collection of contributions by experts in arterial conduits. It is divided into sections, each dealing with a different aspect of the use of conduits, with particularly helpful details on surgical anatomy and technique, as well as useful practical hints and pitfalls. Aspects of the molecular biology and pharmacology of conduits are also discussed, and while these might not appear to be of interest to practising surgeons, they will be attractive to researchers and undoubtedly enhance the academic value of the book. The volume is both well thought out and well written, with adequate illustrations and several excellent reference sections. Some of the chapters rely heavily on personal experience and are styled in the manner of presentations at scientific meetings; publication in this form is reminiscent of symposia proceedings. This, however, is an inevitable consequence of a multiauthor book and the editorial desire to achieve overall excellence.

This volume will appeal to experienced and trainee surgeons alike, and will be a useful source of reference for students of myocardial revascularization. One mild criticism is that different conduits and their uses are not put in perspective in terms of order of preference. Nevertheless, the book is an interesting and useful addition to existing texts on myocardial revascularization, as it gathers together current uses of arterial conduits, including some of which there is little experience.

K. Moghissi
S. Griffin

BUPA Hull and East Riding Hospital
Lowfield Road
Hull HU10 7AZ
UK

Interventional Breast Procedures

D. D. Dershaw (ed.). 262 × 208 mm. Pp. 179. Illustrated. 1996. Edinburgh: Churchill Livingstone. £45.

This slim, liberally illustrated book on contemporary breast imaging has been published at just the right time for it to be relevant to all the disciplines involved in delivering breast care, including health service purchasers. In his preface, Dr Dershaw indicates that he has intentionally included diverse opinions of different contributors to convey the present status of different procedures. This enhances the usefulness of the book, by demonstrating that similar ends can be achieved by different means. This content enhances choice, giving options for both small and large, for the cash strapped as well for the well endowed. The evolution of breast imaging over the past two or three decades is alluded to in the introduction as the rationale for this book. Not only does the content convey to the reader this 'remarkable metamorphosis', it opens up a vision of how breast imaging currently can (and arguably should) be an integral part of breast care in the late 20th century. Nuggets of practical information and wisdom are plentiful. Early ones include a review of the history of breast biopsy, with the economics of fine-needle aspiration. While it omits the benefits of immediate reporting, this is referred to later. In his own chapter on percutaneous biopsy, the editor points out that one disadvantage of core biopsy is the inability to provide results on the same day. This is countered by the fact that this technique can confirm reliably a benign diagnosis for lesions which are indeterminate on mammography. Apart from questioning some of the views expressed on management of cysts and nipple discharge, I found the guidelines credible and the recommendations relevant. The book is well concluded by a commendably brief yet informative chapter on medicolegal aspects of interventional breast procedures. In conclusion, this readable, up-to-date volume is recommended reading for any professional currently involved in commissioning and delivering breast care, especially managers, radiologists and surgeons.

P. E. Preece

Ninewells Hospital and Medical School
Dundee DD1 9SY
UK

British Journal of Surgery 1996, 83, 1662

Notices and announcements

3–8 November 1996
Urogynaecology: Principles and Practice Now
London, UK
Information: Marketing Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

13–16 November 1996
3rd Hong Kong International Cancer Congress and the 7th Epstein–Barr Virus and Associated Diseases Congress
Hong Kong
Information: HKICC Secretariat, 2/F., Professorial Block, Queen Mary Hospital, Hong Kong

14–17 November 1996
3rd Congress of the International Association of Gerontology. European Region – Clinical Section
Thessaloniki, Greece
Information: Athos City Congress, 5 Agias Sofias Street, Thessaloniki 54623, Greece

18 November 1996
Liver Symposium
London, UK
Information. Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

18–20 November 1996
Screening for Breast Cancer Multi-Disciplinary Course
Nottingham, UK
Information. Nottingham National Breast Screening Training Centre, City Hospital, Nottingham NG5 1PB, UK

18–22 November 1996
Annual Course in HPB Surgery
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

19–22 November 1996
European Course on Laparoscopic Surgery
Brussels, Belgium
Information: Administrative Secretariat, Conference Services, Avenue de l'Observatoire, 3 bte 17, B-1180 Bruxelles, Belgium

20–22 November 1996
Vascular Surgical Society of Great Britain and Ireland 30th Annual Meeting
Bournemouth, UK
Information. Linda de Cossart, Countess of Chester Hospital, Liverpool Road, Chester CH2 1BQ, UK

23–24 November 1996
Transanal Endoscopic Microsurgery
Liverpool, UK
Information. J. O'Leary, Training Manager, MASTER Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

27–29 November 1996
British Association of Surgical Oncology Winter Scientific Meeting
London, UK
Information. Mrs V. Hall, Administrator, BASO, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

4–7 December 1996
6th Alexis Carrel Conference on Chronic Rejection and Graft Atherosclerosis
Banff, Canada
Information: Dr L. C. Paul, St Michael's Hospital, 30 Bond Street, Toronto, Canada M5B 1W8, UK

5–6 December 1996
Lung Volume Reduction for Emphysema. A Multidisciplined Approach
Treviso, Italy
Information: Dr G. Di Falco, 3 Divisione Chirurgica, Ospedale Generale Regionale, 31100 Treviso, Italy

6 December 1996
The Role of the Plain Abdominal Radiograph in the Acute Abdomen
Canterbury, UK
Information: Postgraduate Administrator, Kent Postgraduate Medical Center, Kent and Canterbury Hospital, Canterbury CT1 3NG, UK

12–14 December 1996
The Compartment Syndrome
Ulm, Germany
Information: Dr C. Willy, Oberer Eselsberg 40, 89081 Ulm/Donau, Germany

21 February 1997
Surgical and Medical Management of the Diabetic Foot
Harrogate, UK
Information. Mr D. Berridge, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK

2–6 March 1997
11th Biennial Congress – Asian Surgical Association Congress
Hong Kong
Information: Gloria Wong, Cancer Centre, Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

3–21 March 1997
Hammersmith FRCS Course Part B (Surgery in General)
London, UK
Information: Wolfson Conference Centre, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

20–22 March 1997
Medical Management of Major Incidents
London, UK
Information: Wolfson Conference Centre, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

9–11 April 1997
Association of Surgeons of Great Britain and Ireland Annual Meeting
Bournemouth, UK
Information: Association of Surgeons of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

9–11 April 1997
97th Annual Congress of Japan Surgical Society
Kyoto, Japan
Information: First Department of Surgery, Kyoto Prefectural University of Medicine, Kajii-cho 465, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602, Japan

15–18 April 1997
2nd International and 4th European Congress on Ambulatory Surgery
London, UK
Information: N. Strachan, Kite Communications, The Silk Mill House, 196 Huddersfield Road, Meltham, West Yorkshire HD7 3AP, UK

20–22 April 1997
The Paediatric Oesophagus. An Interdisciplinary Symposium. Main Topic: Gastro-oesophageal Reflux with a Special Interest in Alkaline Reflux
Izmir, Turkey
Information: Professor O. Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, 35100 Izmir, Turkey

16 June 1996
Association of Coloproctology of Great Britain and Ireland Annual Meeting
Edinburgh, UK
Information. Association of Coloproctology of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

Instructions to authors

The British Journal of Surgery publishes original articles, reviews and leading articles. Short notes, case reports and surgical workshops are also accepted. All manuscripts are submitted to editorial review.

An article is reviewed for publication on the understanding that the work it reports has not been submitted simultaneously to another journal, has not been accepted for publication elsewhere and has not already been published. **Any detected attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** In order to avoid subsequent embarrassment, authors are requested to submit with their manuscript copies of any other papers, either published, in press, or submitted for consideration elsewhere, which relate to the same subject. It is essential that publications or submissions using the same data set should be submitted to the Editors to allow assessment of any potential overlap with the submission to the Journal. The title page should indicate whether the paper is based on a previous communication to a society or other meeting. Articles and their illustrations become the property of the Journal unless rights are reserved before publication.

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A covering letter must accompany all submissions and must be signed by all authors. The covering letter should state whether an abstract of the work has been published and an appropriate reference should be given on the title page. Authors must disclose in the covering letter any potential or actual personal, political or financial interest they may have in the material, information or techniques described in the paper. The decision to publish or withhold such information will be made by the Editor. Sources of financial support for the work should also be acknowledged. The first named author is responsible for ensuring that all authors have seen and approved the manuscript and are fully conversant with its contents. The Journal accepts the criteria for authorship proposed in the *British Medical Journal* (*BMJ* 1994; 308: 39–42). When a paper has many authors, they may be asked to justify the inclusion of all names listed. Results of multicentre studies should be reported under the name of the organizing study group. Methods of recognizing contributors have been proposed (*Lancet* 1995; 345: 668).

Following final approval of articles, authors are asked to submit the accepted version on disk. These should be IBM-compatible. An accurate hard copy must accompany each disk, together with details of the type of computer used, software, and disk system if known. **Do not justify.** Particular attention should be taken to ensure that any articles submitted adhere **exactly** to Journal style in all respects. Please send us digital versions of your figures. Ideally, these should be sent in native format or PICT if created on a Mac, or in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Avoid using tints if possible; if they are essential to the understanding of the figure, try to make them coarse. Further details can be obtained from the publisher. Disks will not be returned to authors.

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The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethics committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication in *The British Journal of Surgery* of any details or photographs that might identify an individual. Evidence of such consent should be submitted with the manuscript.

Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts, which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; 296: 401–5 or the *Annals of Internal Medicine* 1988, 108: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1.00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses **When quoting specific materials, equipment and proprietary drugs, authors must state in parentheses the brief name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal believes that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a abstract of no more than 200 words on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation. **Randomized controlled trials** should be clearly identified as such in the title and abstract.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no abstract is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 400 words (300 if accompanied by a figure), with no more than five references and one illustration

Surgical workshops

These describe technical innovations or modifications that may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4-cm margins. Manuscripts that do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, abstract, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction, methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them

Title page

The title page should give: (1) the title of the article, (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

Abstract

The second page of the manuscript should carry an abstract of not more than 200 words. This should be broken into four paragraphs each with a clear heading as follows *Background:* this should state why the study was done, and its main aim; *Method:* this should describe patients, laboratory material and other methods used; *Results:* the main findings of the study should be stated briefly, including important numerical values; *Conclusion:* the main conclusion drawn from the Results should be stated. Controversial or unexpected observations may be highlighted, but this section should be brief. The summary should identify clearly the nature of the study: randomized controlled trial, retrospective review, experimental study, etc. It should be written in clear prose.

Tables and illustrations

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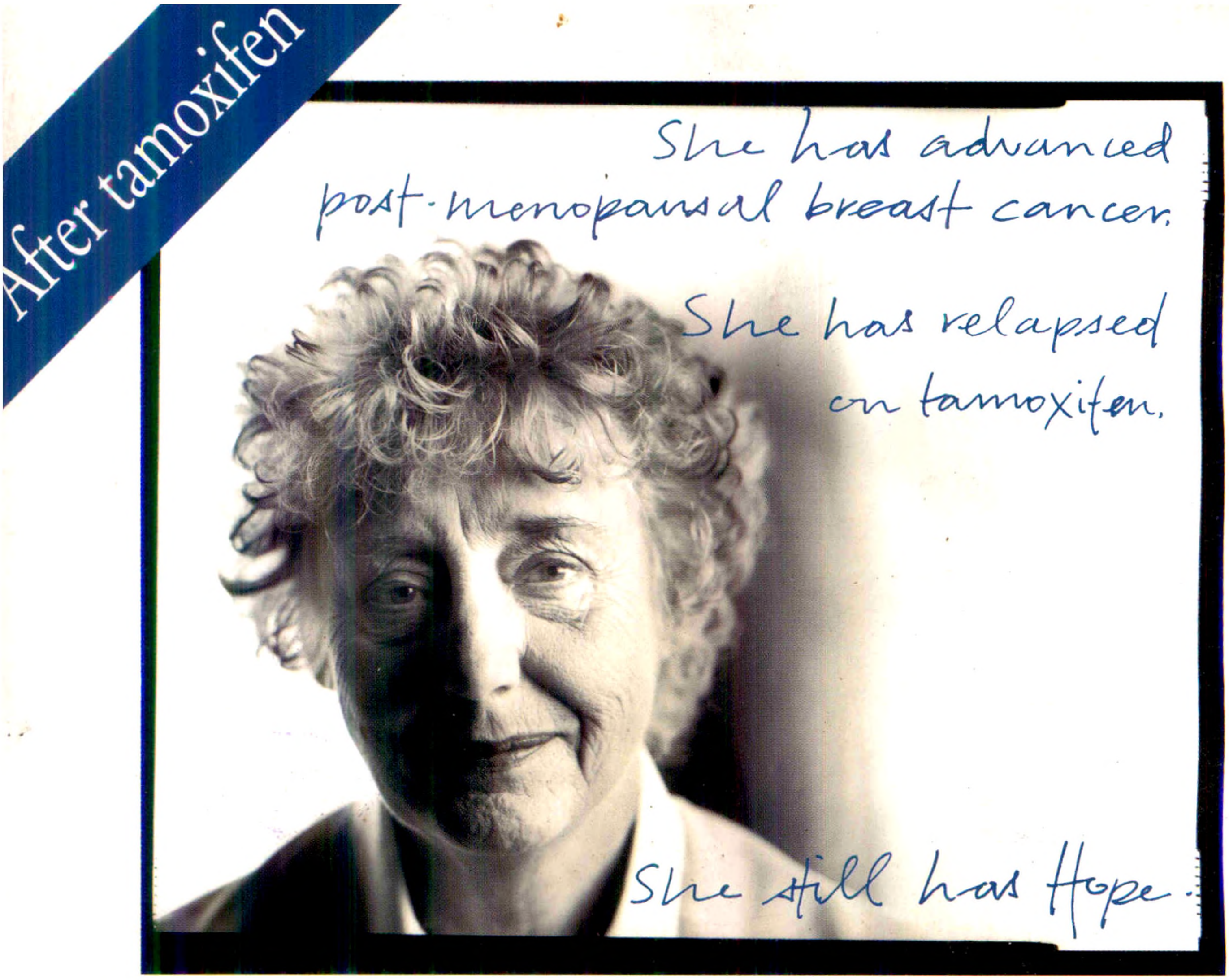
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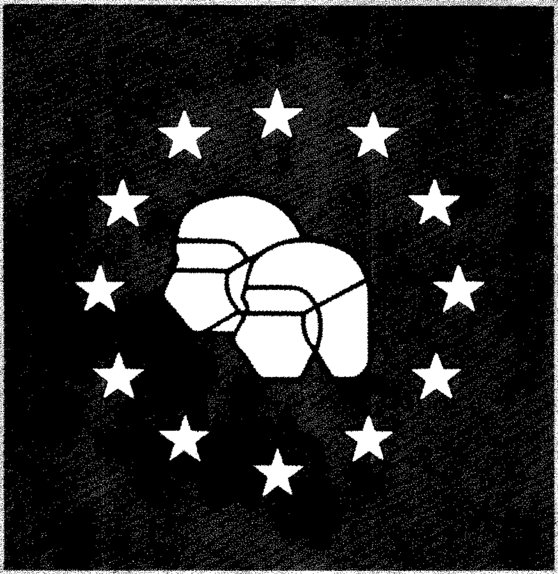

Eurosurgery 96

Sixth European Congress of Surgery
Rome, October 1996

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ISSN 1355-7688

Typeset by RD Composition
Printed by The Friary Press

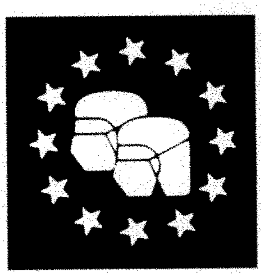
The British

Journal of Surgery

Volume 83 Supplement 2 November 1996

Eurosurgery 96

Rome, Italy
15–18 October 1996



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Eurosurgery 96

This supplement contains the abstracts of papers to be presented during the Eurosurgery 96 Meeting in Rome. The quality of the material to be presented is self-evident from these pages. The abstract selection has been, as usual, rigorous and thorough. The *British Journal of Surgery* is pleased to produce this abstract book as a supplement, as a sign of our continuing association with Eurosurgery.

The Journal wishes every success to the combined meeting of Eurosurgery 96 and the Italian Society of Surgery. The Editors of this supplement hope that all participants have an enjoyable and stimulating meeting.

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Anorectal

Simultaneous treatment of perianal abscess and fistula

A. Caviglia and M. Valle *S. Camillo Hospital,
Circonvallazione Gianicolense, Roma, Italy*

When treating a perianal abscess, excluding the supralevator abscess, when possible we prefer to cure simultaneously both the abscess and the fistula. The procedure rests on the following points. Search for the internal fistula outlet and put a probe in it, if this procedure cannot be carried out we suggest the following alternative procedure.

(a) a small incision of the anal abscess closest to the anus;
(b) aspiration of the pus;
(c) irrigation of the abscess cavity with H_2O_2 (30vol)/H_2O 50 per cent;
(d) check if the H_2O_2 produces any air bubbles in the anal canal

The air bubbles are proof of the existence of the anal fistula and in some cases it is possible to insert a probe. Another procedure utilizes methylene blue.

If it is not possible to insert the probe internally through the fistula from the anal canal, one must try to insert the probe through the abscess cavity Extreme care must be used in this second case as there is high risk of generating a 'false fistula' At this point it is necessary to evaluate the extent to which the external and internal sphincters are involved, the location of the fistula (anterior-posterior) and patient's sex (male/female)

Anterior fistula: (a) Involvement of the internal and/or external sphincter up to 0.5cm: *male:* cut the fistula, *female.* silk thread; (b) involvement of the internal and external sphincter more than 2cm· *both:* silk thread

Posterior fistula: (a) Involvement of the internal and/or external sphincter up to 1–2cm: *both:* cut the fistula, (b) involvement internal and/or external sphincter more than 2cm: *both* silk thread.

In the postoperative period the abscess cavity is treated with H_2O_2 washings only. The silk thread remains for 9 weeks, after which period it is possible to cut the fistula. When the puborectal muscle is involved it is preferable to treat the section with a slow-cutting rubber thread. We have treated 30 patients (80 per cent of all abscesses) with this procedure. No relapse has been observed within the following 12 months.

Long-term results of the internal posterior sphincterotomy with anoplasty

A. Coda, R. Mattio, C. Benedetto, F. Ferri, C. Filippa and
A. Bona *Ospedale Gradenigo, Divisione Chirurgia, Turin, Italy*

The authors report their experience in the treatment of chronic anal fissures and of anal strictures by internal posterior sphincterotomy with anoplasty (IPSA), as proposed by Parnaud and Arnous in 1968 for all cases of tight and inextensible anus This operation is suitable for direct-vision leiomyotomy and for cleaning of the posterior commissure. It always provides a specimen for pathology. It can be usefully associated with haemorrhoidectomy as described by Arnous, for the removal of the posterior node and for treatment of sphincteric spasm In the period 1986–1996 we performed IPSA in 122 patients (average age 46 years, range 22–83 years, 60 per cent males). In 78 cases IPSA was performed alone, whereas in the other 44 cases this was associated with haemorrhoidectomy. Anal wound healed by the fifth week in 95 per cent with baths. Fifteen patients had some difficulties with continence of flatus in the first 2–5 weeks. For 16 constipated or diarrhoeal patients self-dilatation was prescribed. Only one female continued for 6 months. Thirteen patients eventually recovered. In two patients severe complications occurred: anal stricture required early reoperation. In a third patient the fissure failed to recover. Long-term follow-up of 86 cases with average of 37 months has been achieved (range 6–84 months). Only 2 patients showed persistent, but not disabling soiling. There was no other continence problem. Recurrence rate is 0·8 per cent, severe postoperative complication rate is 1·6 per cent and permanent continence defects rate is 2·3 per cent. Long-term follow-up confirm that results are maintained over time

We believe that overall patient satisfaction is as high as 96 per cent. This procedure has been confined to patients with symptomatic chronic anal fissures and strictures that have failed to recover with non-operative treatments.

Slow sphincterotomy in perianal fistulas

D.C. Deac*, L. Deac†, N. Turdeanu*, C. Bunea*, T Pop*,
D. Chirila* and P. Piso* *5th Clinic of Surgery, Cluj-Napoca,
†Medical Center for Public Health, Cluj-Napoca, Romania

The therapy for perianal fistulas still raises discussion. From the simple fistulotomy to the enlarged fistulectomy with total sphincterotomy, we performed all the known methods, but we could not solve all of our cases The rate of relapses still remains at a high level (20–40 per cent).

Many authors maintain the superiority of sphincterotomy in the healing of fistulas, but also their complications incontinence. Because of this fact, in the last 10 years (1985–1995) we performed a technique of slow sphincterotomy with unresorbable separated threads

The technique, similar to Silvestri's technique, consists of 4–5 unresorbable threads being introduced into the fistula track, these ligatures are staggered with a 4–6 day delay between each, producing the slow sphincterotomy and also draining the possible secretions. We performed this technique in 66 cases from a total of 93 operated perianal fistulas The results were good over time (5 years on average) with only three relapses.

We consider that this technique has good long-term results, without the known problems.

Two-stage fistulotomy in complex anal fistulas: a retrospective review of surgical and functional results

G.P. Ferulano, S. Dilillo, S. La Manna, F. Scala and
G. Coppola *Surgical Oncology, 3rd Division of Surgery,
Faculty of Medicine, Federico II University, via S. Pansini, 5,
80131 Naples, Italy*

Complex anal fistulas according to Parks' classification account for 10–20 per cent of fistula series and are usually difficult to manage. We report our experience of the two-stage fistulotomy.

Material and methods: The record cards of 271 patients (mean age 48 years) who had undergone primary or recurrent surgery for fistula in-ano from 1980 to 1994 were reviewed The operative records identified 49 patients (18·1 per cent) with complex anal fistulas needing to be treated by a two-stage technique of wide laying open of the distal track and application of a nylon Seton around the external sphincter (ES) or the puborectalis, tightened until the ES was divided, or left in place loose until an adequate fibrosis allowed the sphincter cutting.

Results: All patients were followed for 1 year or more to evaluate the results (endoscopy, manometry); 44 of them responded to a call for follow-up 3–4 years later. Fistula persisted or recurred in four patients (8·1 per cent), minor continence disorders (soiling, urgency) occurred in 11 patients (22·5 per cent), none referred to faecal incontinence. Statistical analysis show that the site and the level of the internal opening, but not the way of cutting the ES, influenced the overall outcome.

Conclusions: Failures or continence impairment after two-stage surgery of complex anal fistulas have to be expected The use of the Seton did not prevent some unsuccessful results but never caused severe complications in our experience.

Regional anaesthesia in proctological day-surgery

F. Gabrielli, D. Pisani, M. Chiarelli, T. Di Sibio, P. Goglia, L. Poggi and P. Pietri *Department of General and Thoracic Surgery, University of Milan, Ospedale Maggiore Policlinico, Via F. Sforza, 35, 20122 Milan, Italy*

The posterior perineal block is a regional anaesthesia technique that enables the greater part of anal surgery to be performed under safe conditions, and an early discharge of the patients. In our experience traditional proctological operations can be therefore safely performed. From March 1994 to March 1996, our proctological day surgery service performed 193 operations under regional anaesthesia (posterior perineal block). These included 143 haemorrhoidectomies, 24 lateral internal sphincterectomies for fissures, 17 cases of lay open of intersphincter and low transphincteric fistula, three cases of drainage of anal abscess, six cases of removal of a villous ademonas of 2cm in the lower third of the rectum Sedation of particularly nervous patients was performed 1h approximately before the operation with 10mg diazepam i.m. The mixture used was Lidocaine at 0·5 per cent plus Sodium Bicarbonate 1M and Adrenaline 1:200000. The posterior perineal block is composed of four phases: infiltration of perianal skin (10ml), infiltration of the right/left ischio-rectal fossa (block of pudendal and inferior haemorrhoidal nerves by 20ml for each side), infiltration of retrorectal space (block of ano-coccygeal nerves by 10ml), anterior and posterior intradermal infiltration (block of superficial nerves by 10ml) In addition usually we make the infiltration of the haemorrhoidal pedicles with 10ml of anaesthetic mixture. The quantity of anaesthetic adopted varied from 60 to 80ml (average 70ml). Operation time (including anaesthesia administration) was between 30 and 90min. No local or systemic complications were observed during or after surgery that could be attributed to the anaesthetic mix. Four classes have been defined to assess the effectiveness of the anaesthesia: (a) optimum analgesia, (b) satisfactory analgesia that allows the operation to be performed correctly; (c) poor analgesia, operations for which the anaesthetist administered intravenous analgesic drugs (Fentanil); (d) operations involving conversion to general anaesthesia. Of our patients 79 were listed in Class A (40·9 per cent), 98 in Class B (50·8 per cent), 16 in Class C (8·3 per cent), 0 in Class D (0 per cent). It is the surgeon who, after having changed the dressing and checked the patient 2–3h after the operation, is charged with deciding whether or not the patient should be sent home (outpatient) or admitted for the night (inpatient). As far as postoperative pain is concerned, a valid postoperative analgesia lasts 4h at least; afterwards, 181 patients (93·8 per cent) made use of FANS parenterally or by mouth. Eleven patients (4·7 per cent) had problems of postoperative diuresis: five needed catheterization and two reported 4-day urinary retention. In 170 cases (81 per cent) patients empty their bowels after 24–48h, 23 patients (11·9 per cent) need cathartic treatment after 3 days. Many are the advantages offered by the method of regional anaesthesia in day surgery. Above all, it seems to guarantee effective analgesia during the operation. Sphincter relaxation is satisfactory and it is comparable to that obtainable under general anaesthesia. In fact, 15min after the block we can see that the inferior edge of the external sphincter rises and at the same time the inferior edge of the internal sphincter slips caudally: this double and coaxial dislocation of the two sphincters is a guarantee of sphincter relaxation and allows easier retrieval of the intersphincteric space. What counts most is that with a posterior perineal block there is no danger of vagal reflexes during sphincter stimulation and dilation manoeuvres that simple local anaesthesia can never eliminate completely. Furthermore, it must be stressed that postoperative analgesia is effective and long-lasting and there is less risk of urinary retention some hours after the operation. As a result, dismissal can be sooner. The posterior perineal block allows the patients to be operated on while awake and there is no need for long-term hospital recovery

Radio-chemotherapy and transanal excision in the treatment of the anal canal tumours

M. Indinnimeo, S. Brozzetti, C. Cicchini, A. Stazi, C. Nagar, A. Vecchione and G. Fegiz *First Department of Surgery, University 'La Sapienza', via del Policlinico 155, 00161 Rome, Italy*

Between July 1986 and January 1996 eight patients, seven (88·8 per cent) females and one (11·2 per cent) male, affected by anal canal tumour were evaluated. The average age was 57·8 (range 48–69) years. The tumour was squamocellular carcinoma in two patients and cloacogenic carcinoma in six patients The median follow up has been 4 years (range 3–5 years). Three tumours classified as T2N0 have been treated by pre-operative radio-chemotherapy (30Gy in one case, 60Gy in the others and infusion of 5-fluorouracil and mytomicin C) and following transanal excision. In the case treated by 30Gy residual tumour has been histologically found in the specimen. As the excision was complete, this patient did not receive additional radio-chemotherapy, but a rectal prolapse developed, and was treated by surgical intervention. The histological examination of the other specimens was negative for residual tumour. In one patient a bleeding ulcer remained, which was treated by haemostatic stitches. Three tumours classified as T3N1 and two tumours classified as T3N0 have been treated only by radio-chemotherapy (60Gy and infusion of 5-fluorouracil and mytomicin C). These patients treated only by radio-chemotherapy have been evaluated by transanal ultrasonography and anoscopy with multiple full-thickness biopsies by Tru-cut needle every 3 months in the first year and every 4 months in the following years. The Tru-cut needle biopsies have allowed us to exclude residual or recurrent tumour in the areas of postradiation fibrosis. All the patients are alive and disease free at least at 3 years. No patient developed anal incontinence.

Microbiological examination of pus from anal abscesses and fistulas

I.G. Karaitianos, A. Karaitianou-Velonaki, K. Tsamakidis, G. Plataniotis, E. Chinou, E. Skouteli and P. Golemati *Surgical Gastroenterology and Microbiology Departments, 'St Savvas' Hospital and Hellenic Centre for the Control of Special Infectious Diseases, Athens, Greece*

Pus collection in the anorectal and perianal area, either in the form of abscesses or fistulas, presents a difficult diagnostic and therapeutic problem. The aim of the present study was to isolate the infectious agents in these cases and to investigate the origin of infection in order to determine the treatment strategy.

Pus cultures, both aerobically and anaerobically, from 63 patients were studied. Pus was collected from 47 patients with drained abscesses and from 16 patients with anal fistulas. From the 47 specimens collected from drained abscesses, five (after culture for 48h) yielded no bacteria in culture, possibly because of previous antibiotic treatment, in 31 specimens bowel-derived organisms were isolated (*E. coli*, *Enterococcus* spp, *Bacteroides* spp), while from 18 specimens, skin-derived germs were also isolated (*S aureus*, staphylococci). From the 16 specimens collected from anal fistulas, one yielded no growth while in the remaining 15 specimens bowel-derived organisms were isolated. In this group, skin-derived organisms were isolated in only one case. Among the skin-derived organisms, *S aureus* was the most common agent (8 cases), while from the bowel-derived organisms *E. coli* was the predominant one

The above results suggest that the difference in the predominance of the causative micro-organisms reflects different site of origin and the proper therapeutic strategy (either medical or surgical) has to be applied accordingly.

Our experience in ulcerative proctitis

S. Karentzos and I. Kolovou *B' Department of Surgery, G.H. Patission, 15–17 Halkidos str., Athens, Greece*

The purpose of this study was to report our experience in ulcerative proctitis. Ulcerative proctitis is defined as ulcerative colitis confined to the rectum. Thirty patients who had ulcerative colitis had a colonoscopic examination during the attack. Of all patients, 30 per cent had the disease confined to the rectum Another group of 20 patients with proctitis had a colonoscopic and rectoscopic examination and in 5 per cent the biopsy proved ulcerative proctitis, without extensive ulcerative colitis. A number of exogenous factors (acute infections, non-steroidal anti-inflammatory drugs, cigarette smoking, pregnancy and stress) were registered in our patients There was no relationship between the presence of ulcerative proctitis and cancer in our patients. In the world literature the risk of cancer in ulcerative proctitis is different from that in extensive colitis

The treatment was conservative with 1·5 g 5-ASA suppositories per day. Rectal biopsies were performed after the treatment. Surgical therapy was not necessary.

The conclusion is that ulcerative proctitis is a clinical syndrome of ulcerative colitis limited to the rectum. The use of 5-ASA suppositories is effective maintenance therapy. Colectomy is rarely performed.

Pseudo-continent perineal colostomy after abdomino-perineal amputation: a prospective study on 37 patients

P. Lasser, A. Bolognese, D. Elias, S Bonvalot and P. Rougier *Service de Chirurgie Digestive, Institut Gustave-Roussy 39, rue Camille Desmoulins, 94805 Villejuif Cedex, France*

From February 1989 to 1994, 37 patients with a perineal colostomy (PC) using a free autotransplant of smooth muscle according to Schmidt after radical rectal excision for cancer have been studied. These represent 30 per cent of rectal excisions for cancer performed during the same period. No mortality was observed in these series. Four patients developed perineal infection, two perineal dehiscence and three mucosal prolapse. In two patients PC was turned into an iliac colostomy for complications, one infected necrosis and one perforation. Five patients developed pelvic recurrence, diagnosed early in three of them by exploration of the PC. Functional evaluation has been carried out in 35 patients (mean follow-up 33 months) using the Kirwan classification: stage A 2, stage B 22, stage C 9, stage D 0, stage E 2 due to pelvic postradiation injury. Thirty patients were satisfied or very satisfied with the PC.

In selected patients PC use of a free autotransplant of smooth muscle ensures good continence and a normal social life. The need for postoperative radiotherapy or inability to sustain adequate colonic irrigation are contraindications for this technique

Fistulotomy vs fistulectomy for fistula in ano

J.S. Leite, H Eickhoff and F. Castro-Sousa *Serviço de Cirurgia III, Hospitais de Universidade de Coimbra, 3049 Coimbra, Portugal*

For low trans-sphincteric anal fistulas laying open and fistulectomy are widely practised The aim of this study was to ascertain the best of these options.

Materials and methods: The low trans-sphincteric anal fistulas operated on from 1982 to 1994 were analysed by questionnaire and also clinical examination if some abnormality was reported. Fistulotomy or fistulectomy was performed depending on the surgeon's preferences. Time of wound healing, recurrence of fistula or of abscess, and incontinence were analysed with a minimum follow-up of 2 years The results were compared using the χ^2 test.

Results:

		Fistulotomy (n = 23)	Fistulectomy (n = 38)	P
Time of healing (days)		43 ± 20	57 ± 40	n s.
Recurrent fistula or abscess		2	7	n s.
Incontinence	minor	2	7	n s.
	major	—	1	

Conclusion: (a) No clear benefits were found using fistulotomy or fistulectomy; (b) For low trans-sphincteric anal fistulas we recommend the laying open technique instead of the more tedious practice of excision

Progressive anal dilation in the treatment of puborectalis syndrome (PRS)

G. Maria, G. Brisinda and I.M. Civello *Department of Surgery, University Hospital 'Agostino Gemelli', Catholic University, Largo Agostino Gemelli, 8, 00168 Rome, Italy*

Purpose: Functional chronic constipation due to outlet obstruction is mainly caused by puborectalis syndrome. PRS then, although simple to diagnose, has always been difficult to treat. This study aims to assess the ability of progressive anal dilatations to improve frequency of spontaneous bowel movements in patients with PRS.

Patients and methods: Thirteen patients (nine females and four males; mean age 37 years) with severe chronic constipation 'outlet' kind were studied in our Colorectal Unit. Diagnosis was made with physical examination, barium enema, colonoscopy, colonic transit time study, anorectal manometry (ARM), and defecography (DG). Defecography in all 13 patients studied evidenced an increased activity of puborectalis muscle and a failure to expel rectal contents during defecation. We treated the 13 patients with progressive anal dilation. Daily introduction of the three dimensions of dilators (20, 23 and 27 mm diameter) for ten minutes each from the smaller to the bigger was performed for a 3-month period. None of them complained of incontinence.

Results: The clinical results are shown in Table 1.

Bowel movements per week	Before	After	*P*
Spontaneous	0·15 ± 0·37	6·23 ± 4·10	<0·0001
Laxative assisted	4 61 ± 2 63	0·15 ± 0·37	<0·001
Enema assisted	2·30 ± 2·32	0·23 ± 0 43	<0·01

The results of ARM during straining, and the anorectal angle grades at defecography are shown in Table 2.

	Before	Half	End	6 months after	*P*
ARM	93·1 ± 28·9	77·7 ± 20 1	56 9 ± 14·4	62·3 ± 15 3	<0 01
DG	95·4 ± 5·9	105·8 ± 5·3	114 2 ± 8 4	109 6 ± 10 6	n s

Conclusions: We believe that the use of anal dilators affects not only the internal sphincter muscle but also the external sphincter and puborectalis muscles. Dilators oppose the resting physiological contraction of external sphincter and puborectalis muscles, decreasing the puborectalis paradoxical contraction that characterizes PRS. We now think they can be of great help in the treatment of PRS These objective results are correlated with an improvement of functional examinations. Moreover, the treatment is inexpensive, easy to perform, can be done at home, repeated as many times as needed and can be added to biofeedback training.

Endoluminal ultrasound in the study of anal and perianal pathologies

D. Mascagni, P. Urciuoli, D. Tarroni, F.M. Di Matteo, N. Peparini, V. Di Nicola, G. Greco, K.P. Zeri, P.L. Bianchi, S. Arcieri, G. Mezzetti, S. Lucci and A. Filippini *III Surgical Department, University 'La Sapienza', Rome, Italy*

We introduced the use of endoluminal ultrasound (ELU) in the study of anal and perianal pathologies in 1990 Our purpose is to evaluate the potential role of ELU procedure in this specific field. Patients with anal and perianal sepsis, post-traumatic or iatrogenic incontinence, anal pain and anal cancer were studied.

We employed an US probe with a 7 or 10 MHz transducer that rotates, allowing a 360° view of the wall of the anal canal, internal and external sphincters, ischio-rectal and pelvi-rectal fossas. ELU is executed on an outpatient basis; the patient is examined in Sim's position; the preparation consisting in a simple enema performed 2h before.

Two hundred and twenty patients with anal rectal pathologies were studied with ELU: in particular we examined 97 patients with perianal sepsis, 36 with anal pain, 59 with incontinence (26 neurogenic and 33 post-traumatic or iatrogenic) and 28 with anal cancer.

In conclusion, ELU is a well tolerated, simple, low-cost procedure that, in our experience, turned out to be a promising diagnostic method having a major impact in determining the surgical approach of patients with complex anal fistulas and post-traumatic or iatrogenic incontinence.

Treatment of perianal inflammation (PAI)

R. Maskelis *First Surgery Department, Marijampole Central Hospital, Lithuania*

PAI diseases — paraproctitis (PP) and anorectal fistula (FAR) — form more than 40 per cent of all rectal cases During 1986–1990, 46 patients were operated on, and during the last 5 years twice as many patients were operated on

Emergency cases of PP, where only incision is performed, show unsatisfactory results of higher recurrence levels, and longer duration of treatment As of 1991 the Gabriel technique has been used in acute PP and FAR cases involving intrasphincteric (IS) or trans-sphincteric (TS) abscesses The aim of this method is to abolish all channels connecting external (EO) and internal orifices (IO)

A modified Gabriel operation is used, whereby a finger or surface hook is used to find the IO, then an incision is made on the abscess 3–4 cm, through the anus in PP cases. The abscess cavity is drained and cleaned All tissues connecting the EO and IO from the abscess cavity to the rectum are then opened. In extrasphincteric cases it is not usually possible to excise the IO, so in these cases a synthetic suture is passed through the IO, with which the incised tissues and anal sphincter are tied for the next 3–7 days. If the IO is elevated, this must be performed twice (with a 1–2-day interval). In chronic inflammation cases (e.g. FAR), the channel is marked by colour contrast with methylene blue at the initial stage of the operation.

Between 1991 and 1995, 94 patients were treated, with an age range of 23 to 70 years. The modified Gabriel operation was used in 37 patients (39 per cent). The localization of the seat of inflammation, using Goodsall's rule on Stelzner's classification was: anterior wall in nine cases (26 per cent), lateral in two (6 per cent), and dorsal wall in 23 (67 per cent). The duration of treatment in 1991 was 22 days, during which time only two per cent were operated on using the modified Gabriel operation During the last 3 years, this operation has been used on half of the patients The duration of treatment has decreased by a factor of two during the last 5 years, and there are no recurrent cases.

Local transanal excision in rectal cancer

V. Di Nicola, D. Tarroni, D. Mascagni, P. Urciuoli, A. Oddi, L. Greco, C. Nwamba, N. Peparini, F.M. Di Matteo, F. Custureri and A. Filippini *III Surgical Department, University 'La Sapienza', Rome, Italy*

Local transanal excision of rectal neoplasms is indicated in very selected cases. Pre-operative assessment (digital, endoscopic and endoluminal ultrasound examinations) of the stage of the disease is mandatory. Indications for local excision are represented by a proximal margin of the tumour at no more than 8–9 cm from the anal verge, a maximum diameter of the lesion <4 cm, the absence of macroscopic ulceration, a CS 1 clinical stage (according to Mason), a UT 1 ultrasound stage and an extension of the tumour not exceeding a quarter of the rectal wall circumference. From January 1986 to June 1994, 19 patients (7 females and 12 males) with early rectal cancer underwent local transanal excision according to Francillon's technique. The operation was considered curative if: the resected margins were not infiltrated; the staging of the specimen was pT1; the grading of the tumour was G1 or G2 with no lymphatic or lymphovascular invasion. Seventeen patients were staged as pT1; two patients staged as pT2 were proposed for abdomino–perineal resection, but only one underwent Miles's operation because the other refused. The 17 patients are all alive with a follow-up that varies from 1 to 9 years Local transanal excision is an effective sphincter-saving procedure for low rectal tumours and can be considered oncologically curative when a strict selection of indication is respected.

Conservative and surgical treatment of traumatic faecal incontinence

A. Oggianu, L. Basso, C. Bottini, C. Mattana and M. Pescatori *Coloproctology Unit of Rome, via L. Badio 58, Rome 00191, Italy*

Aim: To assess the efficacy of various treatments for faecal traumatic incontinence (FTI). From 1984 to 1995, 498 patients with anal incontinence were observed. Of these, 180 (36 per cent) suffered from FTI [56 males (31 per cent) and 124 females (69 per cent)]. In 39 patients (22 per cent) there was a history of obstetric trauma (episiotomy in 21), in 117 (65 per cent) of anal surgery (74 for haemorrhoids or fistula-in-ano). In seven patients (4 per cent) a combined obstetric-surgical injury had occurred, and 17 subjects (9 per cent) had suffered from a direct accidental trauma. We treated 118 patients (65 per cent). Of these, 21 (18 per cent) underwent only medical and dietary measures, and 47 (40 per cent) rehabilitation by means of pelvic floor exercises, biofeedback, and electrostimulation. Surgery was performed in 50 (42 per cent) subjects, sphincteroplasty being the most commonly employed procedure (23 patients). Mean follow-up was for 28 months (range 2–108 months). Of the 77 subjects studied at follow-up, 44 were affected by moderate FTI, and of these 12 had received medical and dietary measures, 19 rehabilitation, and 10 surgery. The remaining 33 presented severe FTI, and of these five had received medical and dietary measures, 11 rehabilitation, and 16 surgery. After medical therapy, 13 patients recovered or improved, while two remained unchanged, and other two worsened. After rehabilitation, 21 subjects recovered or improved, while eight remained unchanged, and one other worsened. After surgery, 19 patients recovered or improved, 11 remained unchanged, and none worsened. In conclusion, this study shows that satisfactory results can be achieved in the management of FTI if the appropriate therapy is selected and modulated to the single patient.

Elective ambulatory surgery in proctology

M.A. Prieto Reyes, J. Vásquez Márquez and J. Moreno Juliá *Unidad de Proctología. Hospital Reina Sofia, Córdoba, Spain*

The reduction of the hospital stay of patients treated surgically for proctology is an attractive alternative that lowers cost without increasing morbidity, as has been demonstrated in the USA, but its use in Spain is limited. The objective of the present retrospective study is to present our experience in the ambulatory surgery proctology.

Methods: Between 1990 and 1995, there were 1423 operations of ambulatory proctological surgery, 900 (63·2 per cent) men and 523 (36 8 per cent) women, with a mean age of 42 years (range: 13–85 years), *ASA* I = 284, II = 925, III = 214; *anaesthesia.* local 35 (2·5 per cent), general 295 (20·8 per cent) and epidural 1093 (76·7 per cent); *indications:* haemorrhoids 586, anorectal fistulas 438, anal fissure 566, pilonidal cysts 270, papillitis 250 and condyloma acuminatum 4, *technique:* haemorrhoidectomy 586, sphincterotomy 276, fissurectomy 244, anal dilatation 46, fistulectomy (total 213, with Seton 225), open excision (pilonidal cysts 270, condylomas 4). After the surgical procedure, the patient is taken care of for a short time

Results: In our series of 1423 patients, only four patients (0·28 per cent) had some complication and required hospitalization for bleeding and headache. Mortality was nil. Ambulatory surgery saves money· US$2,390,640 (9961 stay days) Our patients [1309 (92 per cent)] believe this surgery is an advancement and a model for the future

Conclusion: Many patients with anal disorders can benefit from the operative treatment in an ambulatory setting, whenever these procedures can be performed without complications, achieving high patient acceptance

Performance protocol in disorders because of surgical treatment of rectal carcinoma

A. Zazo Romojaro, I. Rodriguez, E. Buendia, A. Sampietro, A. Fernandez Duran and C. Ugena *Hospital General La Mancha centro, Servicio de Urologia, Av. de la constitucion Nº 3 Alcazar de San Juan 13600 Ciudad Real, Spain*

Urogenital (UG) disorders can be frequently found in the postoperative period of rectal cancer.

Materials and methods: From January 1992 to December 1994, 79 patients were studied (43 males and 36 females) with a mean age of 66 years (47–87 years) The mean follow-up was 2 years. We asked about possible UG disorders due to surgical treatment of rectal adenocarcinoma.

Results: Forty-two cases were abdominoperineal resections and 37 were low-anterior resections. Duke's classification was: 12 were stage A, 32 B, 21 C and 14 D. During the follow-up 29 patients presented with recurrence, of which only five needed delayed surgery, 13 patients died and 37 were free of tumour 2 years later Some patients had non-urological symptoms: faecal incontinence (1), intestinal obstruction (1), dyspepsia (1), skin irritation because of colostomy. Thirty-one patients presented UG symptoms: 12 dysuria, nine urinary tract infection, four with symptoms because of benign hyperplasia of the prostate (BPH), two acute urinary retention, one urinary incontinence, four obstructive uropathy post-radiotherapy, 14 impotence. These disorders usually occur in the immediate postoperative period. Two patients needed surgical treatment because BPH and three cases urinary derivation because of obstructive uropathy. The rest of the patients were managed with medical treatment. Now we are including a pre- and postsurgical questionnaire into a global performance protocol.

Conclusions: (a) UG disorders are frequent in anal-rectal pathology; (b) some UG symptoms have medical treatment; (c) the use of protocols can help us in the diagnosis and treatment of this pathology.

Perirectal graciloplasty: a novel technique for the evacuation of the neurogenic and inert rectum

A. Shafik *Department of Surgery and Experimental Research, Faculty of Medicine, Cairo University, Cairo, Egypt*

A novel technique for evacuation of the denervated rectum was carried out on 11 mongrel dogs (mean weight 15·8 ± 4·6kg). The gracilis muscle was mobilized from the thigh, pedicled on its origin from the public ramus, and was introduced into the ischiorectal fossa through a para-anal incision. The abdomen was opened and the rectum mobilized and wrapped with the gracilis muscle which was pulled through the ischiorectal fossa into the pelvis Rectal denervation was induced by bilateral pelvic ganglionectomy; cystostomy was performed due to the resultant vesical denervation. Two electrodes were sutured to the gracilis muscle and connected to a myostimulator. The effect of electrostimulation of the gracilis muscle on the rectal and rectal neck pressures and on balloon expulsion was determined Gracilis muscle stimulation with a burst of 30Hz during 300ms with a stimulus of 0·5ms and an intensity just suprathreshold effected a rectal pressure rise ($P < 0{\cdot}001$) with no rectal neck pressure change ($P > 0{\cdot}05$); balloon expulsion occurred at a mean balloon filling of 14 8 ± 3·2ml. Gracilis muscle transposition could be a suitable experimental model for evacuation of the neurogenic rectum. The technique might be considered for the treatment of the neurogenic rectum, or rectal inertia.

Mucosal plication in the treatment of partial rectal prolapse: results of a technique

A. Shafik and O. el-Sibai *Department of Surgery, Faculty of Medicine, Cairo University and Menoufia University, Egypt*

A technique is presented for the treatment of partial rectal prolapse. Fourteen patients (10 women and 4 men; mean age 44·6 years) were included in the study The prolapsed mucosa was protruding outside the anus in six patients and was inside the rectal neck in eight. A mucosal plication operation was performed. The prolapsed mucosa was reefed by multiple vertical purse-string sutures Associated haemorrhoids and anal fissures were dealt with. The patients were followed up for a mean of 31·6 months Straining at stool disappeared No recurrence of mucosal prolapse occurred The technique is simple, easy, cost-effective, and had no complications and can be performed on an outpatient basis.

Surgery for perianal fistulas in Crohn's disease

G. Stabile, A. Basoli, S. Minervini and V. Speranza *II Clinica Chirurgica, Policlinico Umberto I, Rome, Italy*

Perianal fistulas are frequent in Crohn's disease and opinions vary on the best surgical approach. Thirty-seven patients (15 females, 22 males) with Crohn's disease who had surgery for perianal fistulas between 1988 and 1993 were reviewed Mean age was 45 years (range 27–78 years), mean age at onset of symptoms was 37 years old (range 19–62 years old) and mean age at surgery was 43 years old (range 25–72 years old). Follow-up ranged from 2 to 6 years (mean 3 years) Twenty-seven patients had low perianal intersphincteric fistulas and 10 patients had high transsphincteric, suprasphincteric or extrasphincteric fistulas Twenty-seven patients with low fistulas were treated by laying open, with permanent healing in 23, four had a wound infection which required drainage and two of these complained of minor incontinence. Ten patients with high fistulas underwent long-term seton drainage with satisfactory healing in seven patients, recurrence developed in one patient and an insertion of an additional seton was required; only two patients had a proctectomy for non-healing perianal fistulas and severe proctitis. Surgery for perianal fistulas in Crohn's disease has satisfactory results and proctectomy is rarely necessary Laying open and seton insertion are worthwhile procedures Proctectomy is often indicated because of the combination of intractable rectal inflammation and perianal disease rather than perianal disease alone.

Anal ultrasound in the evaluation of perianal abscesses and fistulas

A. Stamatiadis, P. Ioannidis, B. Mylonakis, B. Pararas and M. Filippakis *5th Surgical Department, Evgenidion Hospital, Athens University, Greece*

We report our experience concerning the contribution of anal ultrasound to the assessment of perianal sepsis Anal ultrasound was performed with a hard-cone modification of the rectal ultrasound apparatus. Between 1995 and 1996, 26 patients with perianal abscesses and fistulas were examined ultrasonically. There were 11 patients with recurrent fistulas, seven patients with simple fistulas, three patients with chronic postoperative pain due to residual perianal sepsis, three patients with a primary perianal abscess, one case of rectovaginal fistula and one case of abscess in a sphincteroplasty wound. Abscess cavities were identified as echo-poor cavities occasionally containing hyperechoic areas, while fistula tracts were visualized as hypoechoic bands. In difficult cases, hydrogen peroxide injection in the external opening was most helpful in defining fistula tracts. The ultrasound reports were compared with the operative findings In all cases except one, the anatomic relationship of fistula tracts and abscess cavities with the sphincter muscles was clarified and internal openings were correctly identified. In three cases coexistant postoperative damages in the sphincters were detected.

The surgical treatment of complete rectal prolapse: early- and long-term results

W. Tolwinski, H. Dadan, B. Zalewski, R. Bandurski and D. Cepowicz *Department of Gastroenterological Surgery, Medical University, Bialystok 15-276, Skłodowskiej 24a, Poland*

We present our results of the surgical treatment of complete rectal prolapse according to Moore's procedure. The operation technique is based on liberation of the rectum and displacing it below the symphysis with extraperitoneal exposure of part of the sigmoid with the rectum. During the last 20 years we operated on 41 patients with complete rectal prolapse. Early- and long-term results are satisfactory. This method may be used in the situation where the prolapsed colon is of a substantial diameter. In women it can be combined with simultaneous anterior fixation of the prolapsed uterus.

In consideration of low recurrence rate (2 per cent), in our opinion, the Moore procedure is worthy of notice

Infrared coagulation in bleeding haemorrhoids

A. Uzunova *Military Medical Academy, Clinic of Gastroenterology, 3, G. Sofiski str., 1606 Sofia, Bulgaria*

Infrared coagulation is very effective in cases of bleeding haemorrhoids, both internal and external. We have treated 30 patients with bleeding haemorrhoids: 20 external and 10 internal. Our patients were graduated by first, second and third group, dependent on the grade of haemorrhoid prolapse. We made five applications in all groups of 0·5–1 sec duration. The bleeding stopped after the third application in 90 per cent (27) of cases and patients reported feeling well.

Appendix

Appendicocutaneous fistula: a rare form of enterocutaneous fistulas after abdominal drainage

G. Bruenagel, P. Decker, K.J. Walgenbach and
A. Hirner *Department of Surgery, University of Bonn,
Sigmund-Freud-Str. 25, D-53105 Bonn, Germany*

Introduction: A rare form of enterocutaneous fistula is an appendicocutaneous fistula, which can occur following acute appendicitis, drainage of a perityphlitic abscess or an appendectomy or in connection with chronic inflammatory bowel diseases or carcinoma. Only a few cases are described in the literature, but there are no reports about an appendicocutaneous fistula caused after abdominal drainage.

Case report: In this report we describe the surgical treatment of an appendicocutaneous fistula caused by a simple abdominal drainage, after an extensive pyelotomy for urothelial carcinoma. The site of the enterocutaneous fistula was the same site as the postoperative drainage The fistula was present for 1 year After an injection of contrast solution into the enterocutaneous fistula, we saw a fistula track from the skin to the ileocaecal region.

Treatment: During the operation we found that the fistula track was the appendix itself. The treatment was a classical appendectomy. Usually appendectomy is the classical treatment of an appendicocutaneous fistula In the rare case of a secondary appendicocutaneous fistula, caused by a leakage of an anastomosis, it is necessary to resect the entire ileocaecal region.

Conclusion: We demonstrated an appendicocutaneous fistula, a rare complication after simple drainage of the abdominal cavity without any of the above mentioned diseases. The case report should show that in special cases a enterocutaneous fistula could be started from the appendix.

Appendix carcinoids: our experience

P. Esposito, D. Cerbone, F. Russo, L Keller and
G. Cerbone *Department of Surgery, University Federico II and
Department of Emergency, New Pellegrini Hospital, Naples,
Italy*

Appendix carcinoid is not a common disease. The aim of this study is to evaluate our personal case histories. We evaluated five male and 24 female patients (mean age 32 years) Fifteen patients (51·7 per cent) presented with signs and symptoms suggestive of acute appendicitis. In 14 patients (48·2 per cent) the lesions were discovered incidentally. The tumour was less than 1 cm in diameter in 22 patients, between 1 and 2 cm in four patients, and was bigger than 2 cm in three patients. The tumour was located in 16 patients at the tip, in eight patients in the middle third, and in five patients at the base of the appendix. In 20 patients, the tumour was confined to the submucosa, in seven patients the serosa was involved and in two patients, there was evidence of tumour extension into the meso-appendicular fat, including one patient with a tumour bigger than 2 cm and local lymph-node metastases All patients underwent simple appendectomy except one that, with a tumour bigger than 2 cm in diameter with positive lymph nodes in the mesoappendix, underwent secondary right hemicolectomy. Complete follow-up (mean time 27 months) was achieved in 26 patients; one patient was lost and two patients died at 12 and 14 months respectively, from uncorrelated disease The remaining patients remained free of tumour recurrence

The authors conclude that appendiceal carcinoids are rare and most often are asymptomatic Tumours of less than 1 cm are adequately managed by simple appendectomy The appropriate treatment for tumours of 1 to 2 cm continues to be controversial. Right hemicolectomy is recommended for all tumours larger than 2 cm, whereas preference for an aggressive approach should be given in young patients.

Carcinoid tumours of the appendix

P. Krastanov, P. Mitev, I. Iliev and K. Kjossev *Department of
General Surgery, Military Medical Academy, Sofia, Bulgaria*

A retrospective study was undertaken of patients with carcinoid tumours of the appendix based on the data collected in the years 1986–1995 Fourteen patients with histologically confirmed diagnoses were operated on; five were male and nine female (average age 31 years). In six patients the tumours were discovered incidentally while the rest were operated on because of symptoms of actute appendicitis. No metastatic carcinoid tumours and 'carcinoid syndrome' were evident at admission and intraoperatively as well as during the follow-up period.

The size and location of the tumour as well as its penetration and mesoappendical invasion are analysed as the most valuable criteria when deciding on the proper type of the operation. The authors stress upon the need for very accurate definitions when choosing right hemicolectomy and reveal their algorithm of work with patients with carcinoid tumours of the appendix

Adenocarcinoma of the appendix

T. Montariol, N. Bataille, P. Meyrignac, D. Goere, C. Tresallet,
J.P. Lenriot and M. Huguier *Ch. St Germain en Laye 78015,
France and French Association for Surgical Research*

Appendix is an uncommon location for gastrointestinal tract cancer. The aim of this retrospective study was to assess the clinical symptoms and the surgical treatment of the adenocarcinoma of the appendix

Between 1972 and 1984, 32 patients with primary adenocarcinoma of the appendix (excluding carcinoid tumours) were operated on, in 15 surgical centres, 19 males and 13 females with a mean age of 62 years The diagnosis was never made before operation and 26 patients had emergency surgery.

No clinical symptom was specific The most common presenting feature was that of acute appendicitis (21 out of 32). A tumour of the appendix was identified at operation in 16 patients. Twenty patients underwent appendectomy and 12 right colectomy. One patient died 10 days after operation and 16 during the following 5-year period. Twelve deaths were related to cancer recurrence. The survival rate was 52 per cent at 3 years (16 out of 31) and 46 per cent at 5 years (14 out of 31). Survival was significantly better in patient with Dukes A or B1 tumours, than in those with Dukes B2 or C tumours and in patients who underwent right colectomy (9 out of 12), than in those who underwent appendectomy (7 out of 19) 73 per cent *vs* 34 per cent: $P = 0{\cdot}05$.

Primary adenocarcinoma of the appendix should be considered as a colonic adenocarcinoma and treated by right hemicolectomy.

Acute appendicitis: a study on postoperative wound healing

R. Paulikaitė and J. Dargytė *2043 Vilnius University
Emergency Hospital, Lithuania*

Aim: To evaluate the importance of modern disinfectants used in surgical preparation with respect to postoperative wound healing.

Material and methods: In 1995 488 appendectomies were performed We analysed 100 cases. All these patients were operated on because of acute phlegmonous appendicitis. This diagnosis was proved histologically. We divided the patients into two groups of 50 patients each Characteristics of patients· *Group 1* mean age 27·4 (range 16–69) years; 23 females; 27 males; *Group 2:* mean age 28·9 (range 16–63) years; 24 females, 26 males

In Group 1 we used formic acid solution for the surgeons' and nurses' hand preparation, and 5 per cent iodide for patients' abdominal wall preparation In Group 2 we used 'Microshield/Sterisoap' and 'Biotensid' for the surgical hand preparation, and 'Microshield/Dodesept' for washing of the operation field. The duration of operation ranged from 15 to 100 min.

Results: In Group 1 the operative wounds suppurated in six patients (12 per cent). In Group 2 the wounds suppurated in two (4 per cent). It was noticed that the rate of suppurative wounds depended on the age of patients in Group 1· in age range 15–30 years the wounds suppurated in two patients out of 37 (5·4 per cent); 30–40 years one out of 8 (12·5 per cent), 40–50 years one out of 3 (33 per cent); 50–70 years two out of two (100 per cent). In Group 2 the wounds suppurated only in patients in the age group 15–30 years: one out of 32 (3 per cent); and in age group 30–40 years: one out of 9 (11 per cent) In Group 1 if the duration of appendectomy was 15–30 min, then the rate of suppuration was one out of 34 (3 per cent); if 30–40 min, one out of eight (12·5 per cent), if 40–60 min, three out of six (50 per cent), and if 60 min–100 min, one out of two (50 per cent). In Group 2 the wounds suppurated in two patients out of 30 (6 per cent) when the duration of operation was 15–30 min

Conclusion: The modern disinfectant 'Microshield' is more effective than 5 per cent iodide and formic acid.

Chronic right iliac fossa pain treated by laparoscopic appendectomy

M. Pauwels, G. Hubens, W. Vaneerdeweg and
E. Eyskens *Department of Surgery, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium*

Whether appendicopathy is a cause of chronic abdominal complaints remains controversial Laparoscopy offers both diagnostic as well as therapeutic possibilities for chronic abdominal pain. We studied prospectively the role of laparoscopic appendectomy in the treatment of right iliac fossa pain.

Material and methods: Since January 1995 20 patients (16 female and four male) with an age ranging from 15 to 39 years (mean age 24 years), underwent a laparoscopic exploration and appendectomy for right iliac fossa pain The pain existed for at least one month (ranging from 1 to 26 months) with an average of 5·3 months. No abnormalities were found on clinical or biochemical investigations. Preoperative ultrasound was also inconclusive

Results: All procedures were uneventful. Postoperative morbidity was negligible. Follow-up ranged from 3 to 5 months (mean 3·4 months) In nine patients the appendix was caught in peritoneal adhesions. Histological examination showed lymphoid hyperplasia in seven, and fibrous obliteration in two patients. All remained free of complaints. In one patient a very long appendix containing a fecalith was removed with no histological abnormalities. He remained free of symptoms In the remaining 10 patients a completely normal appendix was extracted. No intra-abdominal abnormalities were seen Microscopic examination showed lymphoid hyperplasia in 5 patients, who became free of complaints. In the five others no microscopic abnormalities were seen. In three of these patients symptoms persisted

Conclusion: Appendix pathology was found in 85 per cent of patients with isolated right iliac fossa pain. All these were treated successfully with laparoscopic appendectomy.

Extrahepatic bile-duct cancer: quality of life, short- and long-term results following 118 patients consecutively treated

S. Alfieri, G.B. Doglietto, G. Costamagna, C. Carriero, F. Pacelli, V. Perri, M. Mutignani and F. Crucitti *Department of Surgery, Catholic University, Rome, Italy*

This study was designed to evaluate the effectiveness of a diagnostic and therapeutic approach adopted in 118 patients affected by primary malignancy of the extrahepatic bile duct [78, 15 and 25 patients with tumours of the upper (UP), middle (MI) and distal (DI) portion of the bile duct, respectively] observed in our unit over the last 8 years

After diagnostic procedures were performed (ultrasound examination, ERCP and CT-scan) resectability rates were established as being 11 per cent, 27 per cent and 52 per cent for UP, MI and DI groups, respectively Twenty-five patients underwent surgical resection.

The overall morbidity and mortality rates were 28 per cent and 8 per cent. 62 per cent and 12 per cent for the UP group, 31 per cent and 8 per cent for DI and 0 for MI groups surgically treated. The curative 5-year survival rate was 30 per cent. 35 per cent, 18 per cent and 0 for UP, DI and MI groups. For the remaining 93 patients considered unresectable, stenting by endoscopic means was almost always the only palliative treatment performed. The quality of life evaluated in 68 patients out of 93 was good in 57 per cent of cases, fair in 19 per cent and poor in the remaining 22 per cent. The overall procedure-related morbidity and mortality rates were 13 per cent and 4 per cent The mean survival rate was 9, 6 and 7 months in UP, MI and DI groups, respectively.

The results of the present study demonstrate the safety and efficacy of endoscopic stenting with palliative intent in the management of extrahepatic bile duct cancer in all patients, including the old and frail, while potential cure can only be achieved by radical surgical resection

Long-term follow-up of patients with hepaticojejunostomy and management of late stenosis

A. Muñoz-Calero, A. Louredo, A. Alonso Poza, M. Trinchet, J.L. Escat, J. De Tomas and J. Muñiz *Servicio de Cirugia Gral 1, Hospital Universitario Gregorio Marañon, Dr Esquerdo, 46, 28007 Madrid, Spain*

Aim: The experience with 11 patients followed for more than 10 years after hepaticojejunostomy is analysed. The usefulness of dilatation of hepaticojejunostomy stenoses by percutaneous transhepatic and under direct vision with intraoperative fibreoptic cholechoscopy is also evaluated.

Material and methods: A retrospective study was carried out on 11 patients seen between 1977 and 1995. All patients except one, underwent hepaticojejunostomy with transhepatic tube and mucous jejunal patch (Praderi–Rodney Smith technique) (Table 1).

Results: Three (27 per cent) patients developed stricture of the anastomosis at 1, 9 and 15 years later, respectively. Early stricture was observed in one hepaticojejunostomy anastomosis without transhepatic tube and jejunal patch. They presented as repeated episodes of jaundice and cholangitis. The diagnosis was confirmed by percutaneous transhepatic cholangiopathy (PTHC) and CT scan. Two patients were managed by dilatation of the stricture with Fogarty catheters and Bakes dilators and biopsies were taken under direct vision with the use of a flexible choledochoscope introduced through the loop of jejunum One patient was successfully managed by dilatation of the stricture by PTHC.

Sex	Age	Date of surgery	Time of intubation	Follow-up	Outcome	Technique	Outcome
F	46	Nov 1977	6 months	18 years	well		
F	51	Nov 1978	8 months	17 years	well		
M	56	Feb 1979	9 months	16 years	well		
F	54	Sept 1979	5 months	16 years	well		
F	57	June 1980	12 months	15 years	stricture at 15 years	Dilatation by PTC	well at 1 year
M	54	March 1981	12 months	14 years	well		
M	50	Oct 1982	12 months	13 years	well		
F	54	March 1984	12 months	12 years	well		
M	37	June 1984	12 months	12 years	well		
F	52	Oct 1986	6 months	10 years	stricture at 10 years	Dilatation with cholechoscope	well at 6 months
F	79	Feb 1994	without tube	2 years	stricture at 6 months	Dilatation with cholechoscope	well at 1 year

S sex, F female, A age, PTC percutaneous transhepatic cholangiography

Conclusions: Long-term follow-up has demonstrated that this technique is useful for patients with high stenosis of the hepatic duct. The late stenosis can be managed with less aggressive procedures, such as dilatation without stent placement, once malignancy has been ruled out Intraoperative fibreoptic cholechoscopy has advantages over PTC because it allows visualization of the area of anastomosis and biopsies to be taken.

The role of side-to-side hepato-jejunal anastomosis in the endoscopic era

N. Candeloro, M. Astuni, R. Frau, S. Laganà, M. Cerretelli and M. Filz *Department of Surgery, General Hospital, Salò, Italy*

The authors report a case of Mirizzi syndrome as a cause of intrahepatic lithiasis treated successfully by side-to-side Roux-en-Y hepatico-jejunostomy.

In cases of multiple bile duct stones or intrahepatic lithiasis some authors suggest the utilization of hepatico-jejunostomy on Roux-Y while the jejunal loop brings up the skin permitting the percutaneous endoscopic and/or radiological treatment of retained common bile duct stones

Side-to-side hepatico-jejunostomy ensures efficacious biliary drainage and preserves the common bile duct continuity, permitting the utilization of ERCP in case of residual lithiasis.

This surgical procedure has to provide a wide anastomosis of at least 2 cm and the indications are multiple intrahepatic or extrahepatic lithiasis and common bile duct enlargement. The case of Mirizzi syndrome we observed has been a good indication concerning the described operation for presence of a large colecystic-coledochal fistula, common hepatic duct enlargement and intrahepatic lithiasis The ERCP performed after 6 months pointed out the normalisation of biliary tract, and 15 months after the operation the patient is free of symptoms.

Acute cholecystitis which is the timing of surgical treatment?

P. Capsambelis, E. Palli, G. Konidis, K. Tsagaropoulos, D. Tsoucalas, D. Kosmadakis, B. Glezos and D. Kontostavlaki *Department of Surgery, General Hospital of Zante, Greece*

Acute cholecystitis is one of the most common causes of acute abdomen However, the timing of surgical treatment is controversial.

Material and method: In the last decade (1986–1995) 105 patients (46 males and 59 females) were treated with a diagnosis of acute cholecystitis

Mean age was 68 years, age range 28–92 years. Forty-two of these patients (Group 1) with a mean age of 64 years, were operated within 72h of diagnosis. Eighteen patients (Group 2) with a mean age of 70 years were operated on after 72h of diagnosis, while 45 patients (Group 3) with a mean age of 72 years were treated conservatively.
Results: Morbidity for Group 1 was 11·9 per cent and mortality 0 per cent: 20 out of 42 suffered from perforation of the gallbladder, biliary peritonitis, gangrenous or emphysematous cholecystitis and 22 out of 42 had a thickened gallbladder wall For Group 2 morbidity was 27·7 per cent: one patient died due to sepsis, and mortality 5·5 per cent (5 out of 18) had perforation of gallbladder, gangrenous cholecystitis and empyema and 13 out of 18 had fattening pariets of gallbladder. For Group 3 morbidity was 8·8 per cent and mortality 0 per cent. The post-operative complications were due mostly to respiratory infections, cardiovascular complications and suppuration of the surgical trauma. The average hospital stay for Group 1 was 11·2 days, for Group 2 23·4 days and for Group 3 10·9 days.
Conclusions: Acute cholecystitis has a high morbidity rate, in order to reduce the hospitalization and morbidity we recommend prompt surgical treatment

Endoscopic treatment of bile duct stones in cholecystectomized patients

R. Forlano and G. Bisceglia *Service of Surgical Endoscopy, Division of Surgery, 'Casa Sollievo della Sofferenza', Hospital IRCCS, 71013 San Giovanni Rotondo, Italy*

Endoscopic sphincterotomy is the treatment of choice in retained or recurrent stones of the common bile duct Patients who had undergone cholecystectomy because of gallstones, and in which either upper abdominal pain, acute biliary pancreatitis, jaundice, cholangitis or instrumental exploration (US, i.v. cholangiography, CT) were suggestive of retained or recurrent biliary duct stones, were examined Between January 1989 and April 1996, 120 patients admitted to the Service of Surgical Endoscopy at our Hospital were evaluated (81 females, 39 males, with a mean age of 64 years). Furthermore, 25 cholecystectomized patients had had surgical exploration of the biliary duct. choledochotomy in 15 cases, choledochoduodenostomy in three cases, papillosphincteroplasty in six cases, side-to-side choledochojejunostomy in one case. Nine patients had a T-drain *in situ* at the time of examination. The endoscopic retrograde cholangiography (ERC) was performed in 117/120 patients (97 per cent), with 18 normal findings. Ninety-five patients (79·1 per cent) received complete endoscopic treatment including endoscopic sphincterotomy of the papilla of Vater or balloon dilatation of the stenotic sphincteroplasty; the stones were extracted using a Dormia Basket, largest stones were crushed with a mechanical lithotripter; peroral cholangioscopy was performed in patients with ductal system not certainly judged free of stones The seven patients (5·8 per cent) who did not benefit from endoscopy, including three with failed incannulation of the papilla and four because of the impossibility of extracting the stones, underwent a surgical treatment with choledocholithotomy and a biliary-enteric anastomosis. Six patients had endoscopic complications (6·3 per cent): one patient with digestive haemorrhage from the sphincterotomy was treated with blood transfusions; four patients with acute pancreatitis were treated with medical therapy; one patient with cholangitis was treated with a naso-biliary drainage. No mortality occurred.

Gallstone disease and liver changes

J.A. Pérez García, R. Moreno Otero, O. Blasco Delgado, E. Muñoz, E. Martín Pérez, J. Figueroa Andollo and P. Serrano Sánchez *Hospital Universitario de la Princesa, Diego de León 62, Madrid, Spain*

Aim: To assess the presence and extension of liver disease in patients undergoing cholecystectomy for gallstones.
Material and methods: Peroperative liver biopsy was performed in 50 patients for gallstone disease, age, sex, other disease, distribution of gall stones, clinical presentation and histopathological findings are investigated.
Results: The series included 33 women (66 per cent) and 17 men (34 per cent), with a mean age of 59 years (range 24–80 years). All of them presented with cholelithiasis and 12 (24 per cent), had also choledocholithiasis. Clinical presentation· gallstone colic 23 (46 per cent), acute cholecystitis 11 (22 per cent), obstructive jaundice nine (18 per cent), acute pancreatitis nine (18 per cent). Liver histology was normal in eight (16 per cent) patients; the commonest abnormalities were: non-specific reactive changes 28 (56 per cent), liver steatosis eight (16 per cent), extrahepatic cholestasis six (12 per cent), cholangitis four (8 per cent), pericholangitis three (6 per cent), secondary sclerosing cholangitis one (2 per cent), chronic active hepatitis one (2 per cent). The commonest histological features were: portal fibrosis, chronic inflammatory cells adjacent to bile ductules, proliferation of bile ductules and portal–portal fibrous tracts. Of the patients with choledocholithiasis, 11 (92 per cent) presented alterations in liver histology and they were more severe.
Conclusions: (a) Gallstone disease is frequently accompanied by changes in liver histology, even when there is no choledocholithiasis; (b) hepatic damage is most severe when common bile duct obstruction was present; (c) portal fibrosis, chronic inflammatory cell infiltration, proliferation of bile ductules and portal–portal fibrous tracts are the commonest histological features, (d) pathological mechanisms of hepatic damage in absence of bile duct obstruction have not been established.

Factors predicting choledocholithiasis in patients with chronic calculous cholecystitis

M. Grande, A. Torquati, P. D'Antini and A.M. Farinon
Cattedra di Chirurgia Generale, Università degli Studi di Roma 'Tor Vergata', c/o Complesso Integrato Columbus, via Pineta Sacchetti, 506 Rome, Italy

Aim: To identify by multivariate analysis factors predicting choledocholithiasis in patients undergoing elective cholecystectomy.
Patients and methods: A prospective series of 335 patients who underwent cholecystectomy for chronic calculous cholecystitis has been considered, from 1989 to 1995. The significance of each variable as a potential predictive factor of choledocholithiasis was assessed by the χ^2 test with Yates' correction, Fisher's exact test, and Student's *t*-two-tailed test as appropriate. The factors with a probability of less than 0·01 were that subjected to multifactorial discriminant analysis. Data are presented as mean (SEM) unless otherwise stated. The Biomedical Data Package (BMDP) statistical software was used for the analysis.
Results: On univariate analysis the variables with predictive significance ($P < 0{\cdot}01$) were: serum alkaline phosphatase (X_1) and bilirubin (X_2) level, number of gallbladder stones (X_3), and choledochal diameter (X_4). These four variables were then analysed using the discriminant analysis program. The importance of variables in the discriminant function was evaluated by contribution of the individual variable to total variance. The equation obtained by discrimnant analysis was:

$$\text{Score} = 0{\cdot}002X_1 + 0{\cdot}485X_2 + 0{\cdot}232X_3 + 0{\cdot}220X_4 - 4{\cdot}167$$

The diagnostic score for an individual patient was calculated by substituting the predictive variables in the discriminant equation. The mean scores were 2·457 and −2·457 for patients with and without choledocholithiasis, respectively. The cutoff point that divided patients with and without prediction of choledocholithiasis was 0 (derived from Anderson's theorem). Patients with a discriminant score above the cutoff point were considered to be at high risk of choledocholithiasis. Using this cutoff point, the scoring system showed a sensitivity of 92·9 per cent and a specificity of 99·3 per cent in predicting choledocholithiasis. The relationship between the predicted and observed choledocholithiasis was statistically significant ($\chi^2 = 126{\cdot}6$, $P < 0{\cdot}0001$).
Conclusion: This study does show that the use of multivariate analysis permits an accurate preoperative prediction of choledocholithiasis to identify patients who need preoperative endoscopic retrograde cholangiopancreatography, optimizing its role in the laparoscopic era.

Endoscopic treatment of obstructive jaundice before operation

J. Kalaba, B. Vekic, D. Matijasevic, A. Bajec and D. Radovanovic *KBC 'Dr D. Misovic' Surgical Clinic, Milana Tepica 1, Belgrade, Yugoslavia*

Aim: The aim of this study is to prove the value of ERCP, endoscopic sphincterotomy (ES) and endoscopy treatment of obstructive jaundice before definitive operation.

Methods and materials: From January 1996 to June 1996 we had 82 patients with obstructive jaundice. All of them had routine examinations (laboratory analysis, ECHO, CT, ERCP, ES if necessary) There were 44 females and 38 males, average age 62 ± 5 years.

Results: Our endoscopic findings were.

- cholecystitis cholelithiasis + choledocholithiasis 31 patients (37·8 per cent) (ES removal 28 patients)
- acute pancreatitis and calculus 10 patients (12·1 per cent) (ES and pre-cut removal 8 patients)
- pancreatis C tumour seven patients (8·5 per cent) (three endoscopic prostheses and four patients were operated)
- postoperative choledocholithiasis six patients (7·3 per cent) (ES removal three patients)
- duodenal diverticulum and intradiverticular papilla six patients (7·3 per cent)
- intradiverticular papilla and choledocholithiasis five patients (6 per cent) (ES removal 4 patients)
- bile duct cancer 4 patients (4·8 per cent) (2 endoprosthesis, two patients were operated)
- tumour of the papilla of Vater two patients, sclerosis of the papilla of Vater two patients (ES treated)
- hepatic cirrhosis four patients (4·8 per cent)
- pancreatic cyst five patients (6 per cent).

We performed 43 ES (52·4 per cent), using that procedure to treat the jaundice completely. There were two haemorrhages after ES, which were conservatively treated

Conclusion: ERCP is the dominant diagnostic method in obstructive jaundice, with therapeutic capability, reduced operative duration, complication and risk of mortality.

Complications caused by stone spillage during laparoscopic cholecystectomy

R.D. Lang, M. Sykora and H. Thiele *Surgical Department, Bruchsal Hospital, Gutleutstr. 1–14, 76646 Bruchsal, Germany*

The loss of gallstones during laparoscopic cholecystectomy (LC) is not uncommon The long-term outcome in patients where gallstones were not retrieved is not well defined as yet, but multiple anecdotal reports describe various types of infectious complications with abscess and sinus formation

Between November 1990 and April 1996 a total of 1900 laparoscopic cholecystectomies were performed. In 554 cases (29·2 per cent) of the gallbladder was injured intraoperatively, with stone spillage occurring in 219 cases (11·5 per cent). In 58 cases (3 per cent) not all stones could be retrieved, and were the reason for infectious complications in five patients (0·26 per cent) (Table 1).

Three patients required laparotomy with removal of stones and abscess drainage. In two other cases stone fragments lost during extraction of the gallbladder caused subcutaneous abscess formation All patients had an uneventful recovery after the stones had been removed.

Table 1. Complications caused by spilled gallstones during LC

Case	Acute cholecystitis	Complication	Time after LC
1	no	Subhepatic abscess	43 months
2	no	Subphrenic and subhepatic abscess	52 months
3	yes	Subhepatic abscess	1 month
4	yes	Subcutaneous abscess (periumbilical)	12 days
5	yes	Subcutaneous abscess (periumbilical)	16 days

The following conclusions concerning stone spillage during LC are made: (a) infectious complications caused by lost gallstones are not necessarily limited to the presence of acute cholecystitis; (b) although conversion to open cholecystectomy for the purpose of stone retrieval does not seem justified, every attempt should be made to retrieve spilled gallstones; (c) preoperatively, the patients must be explicitly informed about the possibility of intraoperative stone spillage and the potential complications caused by left gallstones; (d) since abscess formation can occur as a late complication, even up to 4 years after LC, it is important to document stone spillage in the operative report

Management of iatrogenic bile duct strictures

D. Lombardi, I. Auciello, A. Giubileo and A.G.F. Miro
Department of Internal Medicine and General Surgery, Emergency Surgery, School of Medicine, Federico II University of Naples, Via S. Pansini 5 80131, Naples, Italy

In the last two years, in our department, five patients have undergone surgical repair of non-laparoscopic iatrogenic bile duct injury They were three women and two men; the mean age was 51·6 years (range 38–61 years) All the patients were referred to us from county hospitals. In three of them, injuries were recognized early in the post-operative period (bile leak, signs of cholangitis), in one the injury was recognized at the time of the cholecystectomy operation The last, a 58-year-old female, was referred to us because of the presence of hepatomegaly, cholangitis and intrahepatic stones one year after a Roux-en-Y hepaticojejunostomy for a grade IV stricture On admission, all patients had full haematological assessment Radiological investigations included chest X-ray, ultrasound, percutaneous transhepatic cholangiography, endoscopic retrograde cholangiopancreatography. Angiography was not performed because of the absence of a history of vascular damage at operation and because of the absence of signs of liver failure

For all patients, a Roux-en-Y hepaticojejunostomy was carried out and two stents (removed percutaneously 6 months later) were placed at the anastomosis, including the last patient. The post-operative course was normal and all patients were discharged within a month All the patients are under a 6-month follow-up and, so far, no signs of failure of surgical treatment have been found

Although our series is not large and the follow-up is not long enough to evaluate the long-term results of our surgical repair, we are in general agreement with the literature: injuries that are identified postoperatively should be referred to a specialized centre with expertise in hepatobiliary surgery because a failed attempt at repair may seriously compromise the outcome of a stricture, above all of a high one.

Radical surgery for Klatskin tumours

M. Malagó, M. Gundlach, X. Rogiers, A. Bassas, J.R. Izbiki, A. Anselmo and C.E. Broelsch *Universitats-Krankenhaus Eppendorf, Department of Surgery, Martinstr. 52, 20246 Hamburg, Germany*

The results of treatment of Klatskin tumours are relatively poor and even current surgical practice should be considered as a palliative modality. Hilar cholangiocarcinoma spreads along the bile ducts and their periductal lymphatics, thus the oncological approach has limited effect with the classic treatment modalities

At our hospital 80 patients have been treated between 1985 and 1995 According to the Bismuth classification there were 17 Type I and II, 24 Type IIIa and IIIb and 39 Type IV.

		Treatment	Median survival (months)
Group 1	11 (14 per cent)	Endoscopic drainage	11
Group 2	27 (34 per cent)	Exploration and endoscopic drainage	4
Group 3	24 (30 per cent)	Hilar bile duct resection	17
Group 4	18 (22 per cent)	Hilar bile duct resection and liver resection	16

Among the 42 resected patients with R0 resections ($n = 22$) had a median survival of 26 months, R1 or R2 resections ($n = 20$) 12 months, no resections ($n = 38$) 6-month-survival. Further stratification of results showed that no Type IV tumour had a R0 resection. Hilar resection combined with liver resection has the best potential for cure even though the small resection margin accounts for the unsatisfactory outcome.

Based on these results a new programme of aggressive surgery consisting in extended right (REH) or left (LEH) hepatectomy and radical lymphadenectomy has been started. Patients with small left lateral lobes are to be staged undergo a portal vein ligation and hilar resection followed by a REH after 4–6 weeks or alternatively transhepatic portal vein embolization and REH after 4–6 weeks as the left lobe grows in size. Three patients with Type IIIa ($n = 1$) and Type IV ($n = 2$) previously amenable only to non-curative surgery or palliative drainage have been treated in this programme and are alive and well at 5 months. The two patients with Type IV tumours underwent partial portal vein resection.

Aggressive surgical approach which allows achievement of larger resection margins and extirpation of bile ducts and liver tissue in proximity of the tumour is the strategy to achieve better results in the treatment of Klatskin tumours.

Endoscopic sphincterectomy: its advantages and faults

R. Markert, I. Klimczak, J. Wasiak, M. Gryszkiewicz,
J. Korzycki and A. Waniek *I Surgical Clinic of Medicine, University of Łódź, Łódź, Kopcińskiego 22, Poland*

The aim of this study was assessment of complications of endoscopic sphincterotomy which, after all, require the aid of a friendly surgeon.

In the Endoscopic Laboratory attached to the Surgical Clinic 1148 sphincterotomies were performed in the years 1987–1995. They were carried out for choledochal stones in 647 cases, for stenosis of the papilla of Vater in 148 cases and restenosis in six cases, for acute pancreatitis in 66 cases, chronic pancreatitis in 73 cases.

During that time 32 complications requiring surgical intervention were noted, such as bleeding in nine patients, perforation of the common bile duct in one patient, acute pancreatitis in 21 patients and impaction of the Dormia's basket in two patients. Seven patients could be treated conservatively. Four patients died.

The authors discuss the difficulties and diagnostic criteria as well as the methods of surgical management in these patients. They think that endoscopic sphincterotomy constitutes a remarkable advance in the treatment of the common bile duct diseases, but it requires highly experienced endoscopy specialists and cooperation with surgeons sensitive to early diagnosis of possible complications and to their effective treatment

Traditional surgery for common duct bile stones is not an obsolete procedure

F. Nardi, A. Gavelli and C. Huguet *Department of Surgery, Princess Grace Hospital, 98000, Monaco*

Endoscopic sphincterotomy is considered today to be the best therapeutic option for common bile duct stones. However, classical surgical choledocholithotomy is a valuable approach despite its risks in aged patients.

One hundred and thirty-eight cases of choledocholithotomy for common bile duct stones have been prospectively recorded: 61 patients were >75 years old and 43 of them were operated in emergency (70 per cent). In the group of younger patients (<75 years old) only 28 cases (30 per cent) were done as emergencies. Surgical procedure included after cholecystectomy, routine peroperative cholangiography followed by cholangioscopy, choledocholithotomy and external biliary drainage through a T-tube (83 per cent) biliary-enteric anastomosis (17 per cent) or common bile duct primary suture (one case).

Overall hospital mortality was 1·4 per cent. It was nil after elective procedures, whatever the age of the patient. Two patients, both 82 years old, died after emergency surgery. Morbidity was 2·6 per cent in the younger group, *vs* 15 per cent in the elderly. Hospital postoperative stay was 12·4 ± 7·4 days.

In our hands, open choledocholithotomy remains the gold standard in the treatment of common bile duct stones This approach is safe, even in elderly patients, and allows a complete definite therapy of bile stones in a single step procedure. Laparoscopic choledocholithotomy might replace the open procedure in the future, but this new procedure should be evaluated and compared to traditional surgery.

Primary lymphoma of the gallbladder presenting as acute acalculous cholecystitis

E. Garrote Nieto, M.E. Pertejo Muñoz, F. Fdez Ferrero,
J. Boned Purkiss and M.J. Sastre Pérez *Clínica Nuestra Sra. de América, Arturo Soria, 103, 28043 Madrid, Spain*

We report a case of primary lymphoma of the gallbladder that presented as an acute acalculous cholecystitis clinically and after diagnostic imaging. We also wish to mention that extranodal abdominal lymphomas have been reported mostly as highgrade malignancy and originate from B and T cells.

Our clinical case is a low-grade lymphoma with small plasmocyte cells. We review the previous publications, which are very few and varied. We conclude saying that primary lymphoma of the gallbladder is extremely rare as an acute disease.

Our patient did not present with other organs affected, and did not have gallbladder stones. The ultrasound study showed a gall bladder wall thicker than 3 mm. More than 98 per cent of gallbladder neoplasms are adenocarcinomas

Endoscopic endoprosthesis or bypass surgery for palliation of malignant obstructions of the lower biliary tract?

G. Nuzzo, G. Clemente, L. Spina and F. Giuliante *Geriatric Surgery Unit, Catholic University, Rome, Italy*

Endoscopic placement of endoprostheses has become an attractive alternative to bypass surgery for relieving obstructive jaundice in patients with unresectable biliary or pancreatic carcinoma. Some randomized studies[1-3] failed to show significative differences between biliary stenting and surgical bypass regarding survival, complications and costs, taking into account readmissions for blocked endoprosthesis and gastric outlet. Forty-one consecutive patients with obstructive jaundice from unresectable malignancies of the pancreas and the lower biliary tract were admitted at our department between 1988 and 1995. A surgical bypass (hepatico-jejunostomy with gastro-jejunostomy on the same Roux loop, preferably) was performed in 19 patients (12 males, seven females, mean age 65·7 years) without major morbidity and mortality. An endoscopic placement of an endoprosthesis was performed in 22 patients (19 males, three females, mean age 70·3 years) with a 27 per cent morbidity and 9 per cent mortality; four of these patients required, successively, a surgical bypass for repeated episodes (3–7) of cholangitis. The postoperative course was complicated in three of these four patients and one patient died. In this series, a high incidence of procedure-related complications, resulting in failure of palliation, was found following biliary stenting. So, the initial advantage of a shorter hospital-stay was reduced by repeated admission for blocked endoprosthesis. In conclusion, if the primary goal of the palliative therapy is to improve the quality of survival, bypass surgery is more attractive as an initial treatment option. Biliary stenting can be recommended for patients in whom a much briefer survival might be expected.

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An exceptional case of giant cystadenocarcinoma of the gallbladder

A. Oddi, S. Cavalli, C. Iozzia, E. Conti and S. Camera. *Ospedale 'San Lazzaro', Alba U.S.L. 18 Regione Piemonte, Italy*

According to the WHO histopathological classification of the gallbladder and biliary tree neoplasms, cystadenoma is an extremely rare tumour, mainly located in the biliary duct [1]

The malignant equivalent of this benign neoplasm is practically unknown and, to our knowledge, a cystadenocarcinoma of the gallbladder has never been reported in the literature

The patient we are reporting presented at admission a huge abdominal mass, the size of a basketball, mainly located in the right abdominal and epigastric regions and completely asymptomatic

A US study and a CT scan showed a large mass with liquid and heterogeneous content, connected with the gallbladder. No vascular supply was seen on angiograph. Blood tests were within the normal limits and as well as the tumoural markers, with the exception of Ca 19-9 which was 148 U/ml (normal range = 0–37 U/ml) At operation the mass was revealed to be a very large cyst, connected only with the gallbladder, without involving other organs. The patient underwent a mass excision and cholecystectomy. The histopathological slides proved a cystadenocarcinoma.

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Microbiological examination of experimental Roux-en-Y choledochojejunostomies

G. Pósfai*, V. Kovács*, Á. Hernádi*, J. Tóth† and M. Ihász* **3rd Department of Surgery, Semmelweis Medical University, Surgical and †Ophthalmological Department, University of Veterinary Medicine, Budapest, Hungary*

Microbiological examination is difficult to carry out in human practice during an operation of Roux-en-Y choledochojejunostomy

Choledochojejunostomies were performed in Gottingen type minipigs by the help of microsurgical technique using 40-cm long jejunal loops Aerobic and anaerobic cultivations were performed using standard methods from the bile, the area of the biliary, the enteroentero anastomoses, the duodenum and from the eluent respectively of nine animals 20 months after surgery, the colony-forming units (CFU) were determined using dilutions. We found a significant increasing of ciliary and/or anaerobic bacteria in the area of the biliary anastomosis in symptom-free animals.

The 40-cm long Roux-loop does not protect the area of anastomosis from ascending infection. A possible anastomotic stenosis creates the conditions for making facultative pathogens into pathogenic

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Clinically active gallstone disease-related inflammatory and immunological changes in liver

G. Pupelis, K. Arkilins, N. Maracova, V Zalcmane, R. Kleina and M. Mihelsons *Latvian Medical Academy, Riga, Latvia*

During the last few years a significant progress has been made in the investigation of immunomodulation and inflammatory reactions in different chronic and acute liver diseases using immunohistochemical methods. Correlation between expression of adhesion molecules, activation of macrophages and recruitment of leukocytes, monocytes and T lymphocytes in the sites of inflammation has been revealed.

The purpose of the present study was to investigate the expression pattern of endothelial leukocyte adhesion molecule-1 (ELAM-1) and intercellular adhesion molecule-1 (ICAM-1) and morphology changes in liver in cases of active gallstone disease (AGD)

Methods: Liver biopsy specimens from 21 patients with AGD were obtained during cholecystectomy and used for immunohistochemistry, routine histology and ultrastructural investigations The removed gallbladder was analysed routinely for 13 patients who were operated in acute and subacute phases of AGD. There were eight elective operations.

Results: The routine examination of removed gallbladders revealed chronic inflammatory changes in 18 and acute inflammation in three cases. The examination of liver specimens demonstrated lymphocyte infiltration, ultrastructural signs of activation of sinusoidal endothelial and Kupffer cells. Fibrosis in the portal tracts, fatty change and hydropic swelling of hepatocytes were seen Immunohistochemical observations showed that 62 per cent (13 of 21) of the AGD cases expressed ICAM-1. The patterns and the intensity of ICAM-1 expression were related to the degree of hepatocellular damage and parenchymal inflammation No reactivity ELAM-1 was found except in two cases These specimens were taken on the third and the fifth days, respectively, after severe attacks of AGD. No significant correlation between the degree of inflammatory changes in the gallbladder and expression of ICAM-1 and ELAM-1 was found.

Conclusion: In this study correlation between ICAM-1 expression, activation of macrophages and lymphocytes and inflammation activity in liver was found The expression of ELAM-1 and ICAM-1 was similar to patterns reported by other authors in different chronic liver inflammatory reaction and immune response to AGD. ICAM-1, macrophages and other mononuclear cells is likely involved in this inflammatory mechanism. This immune response is not directly related to degree of inflammatory changes in gallbladder.

Acute cholecystitis: time for operation?

M. Ristov, G. Denkov and S. Decovski *Stip Medical Centre, Stip, Macedonia*

Aim: To analyse the results obtained with surgical treatment of earlier operation in acute cholecystitis by comparing them with the results obtained with delayed cholecystectomy

Material and methods: In the period from 1991 to 1995, 248 patients underwent surgery after diagnosis of acute cholecystitis. This represents 18 per cent of all surgery for cholelithiasis performed in our department during that time. Acute cholecystitis was defined as acute symptoms of less than 1 week's duration prior to admission with presence of abdominal pain, nausea and vomiting, fever, jaundice or not, marked abdominal tenderness and mass, leucocytosis and acute pancreatitis or not

All the patients were divided in two groups, in Group 1, 83 patients were operated upon within 72 h of admission (20 males and 63 females, aged range 22–78 years, with majority between 40 and 50) and Group 2, 165 patients with delayed cholecystectomy (28 males and 137 females, age range 19–81 years, with majority between 50 and 60) We studied and compared the following parameters· associated clinical and laboratory findings, treatment, morbidity, mortality and length of hospital stay

Results: The morbidity of the disease included the presence of associated jaundice but did not play a significant role in mortality in mortality in patients operated on immediately, although it may be associated with increased mortality in those patients in whom operation is delayed The incidence of associated pancreatitis was higher in those patients who died or had postoperative complications but was unrelated to the timing of operation Postoperative complications occurred in 6 per cent of the patients in Group 1 and 15 per cent in Group 2. It therefore appears that the use of preoperative antibiotics did not prevent postoperative septic complications, the development of gangrene or perforation of the gallbladder The length of hospital stay was significantly shorter in patients operated on acutely (12 days), compared to those patients undergoing delayed operation (23 days)

Conclusions: A review of 248 patients with acute cholecystitis revealed that early operation for acute cholecystitis is recommended because it effectively reduces morbidity and the length of hospital stay

The role of HIDA scanning with cholecystokinin augmentation in patients with undiagnosed right upper quadrant pain

M.K. Roy, R.J. Delicata, G.W.B. Clark, M.C.A. Puntis, J.I. Rees and P.D. Carey *Department of Surgery & Radiology, University Hopital of Wales, Heath Park, Cardiff CF4 4XW, UK*

Aim: To evaluate the usefulness of HIDA scanning with cholecystokinin augmentation in patients with undiagnosed right upper quadrant pain

Materials and methods: Between January 1993 and December 1995, 32 patients with right upper quadrant pain and normal LFTs, ultrasonography and oesophago-gastro-duodenoscopy underwent HIDA-scanning with cholecystokinin augmentation. Gall bladder ejection fraction (GBEF) was calculated and a GBEF of >35 per cent was considered normal. Delayed appearance of HIDA in small bowel was considered suggestive of sphincter of Oddi dyskinesia.

Results: Patient demographics and management are detailed below:

	Normal HIDA (NHIDA) (n = 17)	Positive HIDA (PHIDA) (n = 15)
GBEF	>35 per cent	≤35 per cent
Median age	52 years	40 years
Cholecystectomy	0	7
ERCP and manometry	1 (sphincterotomy)	3 (awaiting)
Lost to follow-up	1	1

Mean follow-up was 24 months (range 2–96 months). Of the NHIDA group, 11 (65 per cent) patients have had a symptomatic improvement; the single patient with sphincter of Oddi dyskinesia responded successfully to ERCP and sphincterotomy. Of the seven cholecystectomy patients in the PHIDA group, five (71 per cent) are completely pain free, one had partial pain relief and one has developed chronic pancreatitis. Histology of the removed gallbladders showed chronic cholecystitis in all seven.

Conclusion: HIDA-scanning with cholecystokinin challenge is helpful in evaluating patients with undiagnosed right upper quadrant pain and may identify those with chronic acalculous cholecystitis and sphincter of Oddi dyskinesia who would benefit from cholecystectomy or sphincterotomy, respectively

Microlaparotomy cholecystectomy

I.I. Rozsos and T.P. Rozsos *Moritz Kaposi Medical Center, Kaposvár H-7400, Tallián Gy. u. u.20-34, Hungary*

The microlaparotomy cholecystectomy (MLC) is not yet a widespread procedure. In order to elaborate further on the procedure and to demonstrate its true value, 1357 micro- and modern minilaparotomies, without exclusion or selection, were analysed and the operation procedures were then summarized. The operations were completed with microlaparotomy (smaller than 4cm incisions) in 1272 cases (93·8 per cent), with modern minilaparotomies, (4·1–6cm) in 78 cases (5·7 per cent), with conventional mini (6·1–10cm) in four cases, and the incisions longer than 10cm with conventional laparotomies in three instances (0·3–0·2 per cent). We performed a complete cholecystectomy in 98 per cent, a longer cystic stump was left in 1·3 per cent, subtotal and partial cholecystectomies in 0·4 and 0·3 per cent, respectively. In 78 of the cases (5·7 per cent) simultaneous choledocholithiasis was discovered and resolved, 16·5 per cent of the operations were termed as difficult. Two-thirds of the intra- and postoperative complications as well as early reoperations occurred in cases where they followed a delayed operation for obstructive cholecystitis Two patients died (0·14 per cent) due to non-surgical complications These experiences show that cholecystectomy performed by micro- and modern minilaparotomy is a realistic alternative to conventional and laparoscopic cholecystectomy.

Choice of surgery for bile duct carcinoma

M. Safioleas, E. Misiakos, J. Kakisis, E. Evangelidakis, C. Manti, S. Rossonis, D. Katsikas and G. Karatzas *2nd Department of Propedeutic Surgery, Athens University Medical School, Laiko Hospital, Athens, Greece*

The management of bile duct carcinoma remains controversial, with different surgeons supporting radical resection or palliative techniques. The aim of this study is to present our experience in the treatment of bile duct carcinoma comparing the different techniques used. Clinical data from 67 consecutive patients with carcinoma of the extrahepatic bile ducts, treated surgically during the past 25 years in our department, were retrospectively analysed to aid in the selection of appropriate radical or palliative measures Preoperative assessment was directed toward defining site, stage and resectability of tumours. Forty-five patients had tumours involving the upper third of the bile duct, 12 patients had tumours of the middle third and 10 patients had tumours of the lower third. Complete resection of all macroscopic tumour was accomplished in 12 patients (Group 1). In the remaining 55 patients the tumours were advanced with involvement of surrounding structures or distant metastases These patients underwent palliative procedures· cholangioenteric bypass was performed in 14 patients, cholecystoenteric bypass in 5 patients (Group 2: 19 patients), transtumoural intubation alone in 27 patients (Group 3) and biopsy only in nine patients (Group 4). The overall hospital mortality rate was 14·9 per cent. Mean survival time was longer for Group 1 compared to other groups (Group 1: 23 5 months, Group 2: 8·5 months, Group 3: 8 5 months and Group 4: 2 months) There was no difference in postoperative morbidity and mortality and survival between patients undergoing cholecystoenteric or choledochoenteric bypass. In conclusion, aggressive surgical resection, when feasible, offers the best possibility of prolonged survival However, the majority of patients have unresectable tumours at operation and palliative techniques are used to improve their quality of life In special cases of advanced bile duct carcinoma a cholecystoenteric bypass is of great help when a choledochoenteric anastomosis is technically difficult.

Gallbladder carcinoma: retrospective analysis of 60 cases

F. Castro Sousa, H. Carvalho, G. Tralhao and M.G. Jorge *Hospital da Universidade de Coimbra, Serviço de Cirurgia III, 3040 Coimbra Codex, Portugal*

Gallbladder cancer remains a clinical entity of difficult and late diagnosis; surgical resection of the tumour is still the only chance of cure

We have analysed 60 cases of gallbladder cancer (48 females and 12 males) with a mean age of 69 (47–87) years treated between 1962 and 1995; from 1962 to 1988 we treated 29 cases; between 1988 and 1995, 31 patients were treated. Of the patients 78 per cent were older than 60 years The most significant signs and symptoms were abdominal pain (54 per cent), jaundice (51 per cent), biliary dyspepsia (46 per cent) and an abdominal mass (48 per cent). Cholelithiasis was associated in 42 per cent; a correct diagnosis was established before the operation in 17 per cent of the patients; it was a pathological finding in 14 per cent.

All patients were operated on and resection was carried out in 22 (37 per cent): cholecystectomy (n = 8), cholecystectomy + gastrectomy (n = 1), cholecystectomy + appendicectomy (n = 1), cholecystectomy + hepatic segmentectomy (n = 5), cholecystectomy + choledocho-enteric anastomosis (n = 7). The resection was curative in 18·5 per cent of the cases. Mortality was 10 per cent and morbidity was 6 6 per cent; actuarial survival at 5 years was 5·8 per cent (2 patients)

The results of this study seem to confirm that the diagnosis of gallbladder cancer is usually at an advanced stage (although in the last 7 years a preoperative diagnosis was possible in 32 per cent of the patients) and that even an aggressive surgical treatment is not always able to improve significantly in prognosis.

Bile duct ascarials: a rare reason of acute cholangitis

B. Stanslovaitis, A. Razbadauskas, V. Timinskas and D. Razbadauskiene *Klaipeda Seamen's Hospital and Centre of Society Health, Lithuania*

The aim of the study was to describe a rare reason of acute cholangitis Patient DP, a 50-year-old woman, was admitted to our hospital 3 days after the beginning of the illness. She felt a sharp pain in the right hypochondrial area, nausea and had a high fever with shivers The patient was operated on nine years earlier for chronic calculous cholecystitis with choledocholithiasis, and cholecystectomy, choledocholithotomy and choledochoduodenostomy were performed. She felt very well after the operation and this attack was the first. The ultrasound examination revealed the intrahepatic bile duct to be moderately enlarged, with common bile duct about 0·8cm in diameter.

Laboratory data showed leucocytosis (11·2 × 10^9/l) and eosinophilia (22 per cent). At the time of endoscopy superficial gastritis was found and in the duodenum and choledochoduodenal opening was seen with a 5cm segment of rounded helminth coming through it This helminth particularly disturbed the flow of bile and it was removed endoscopically The patient felt well after this procedure and the pain passed Microbiological examination of helminth showed that it was a male *Ascaris lumbricoides* and evaluation of the faeces confirmed that The treatment by Vermox (150mg twice) was effective, the patient evacuated a few helminths in faeces and the pain passed completely. At the time of control ERCP-bile ducts were not enlarged, nor were there any defects of filling The patient was monitored for 1 month: she felt well, and no helminth eggs were found in the faeces

Conclusion: In most cases the cause of acute cholangitis are stones, but we must not forget other causes, such as helminthosis

Management of common bile duct lithiasis in the era of laparoscopic surgery: 282 cases

C.L. Thiry*, J. Vo Huu Le*, N. de Manzini*, S. Rohr*, C. Wantz*, B. Duclos†, R. Baumann† and C. Meyer* **Service de Chirurgie Générale et Digestive, Centre de Chirurgie Viscérale et de Transplantation, †Service d'Hépatogastroentérologie et d'Assistance Nutritionnelle, Hôpital Universitaire de Strasbourg-Hautepierre, 67098 Strasbourg Cedex, France*

Aim: To determine the optimal therapy of common bile duct stones (CBDS).

Patients and method: From January 1990 to December 1995, 282 patients [185 women, 97 men, mean age 58·6 (range 18–92) years] where treated for confirmed or suspected CBDS, representing 17·3 per cent of all biliary lithiasis cases treated during the same time (1625). The clinical presentation was CBDS in 49·3 per cent (139), cholangitis in 17·3 per cent (49), jaundice in 17 per cent (48), and acute pancreatitis in 16·4 per cent (46). Sequential treatment was performed in 70·2 per cent of cases (198), meaning an ERCP with endoscopic sphincterotomy (ES) followed by a laparoscopic cholecystectomy (LC) An immediate laparotomy after an ES was performed or not in 19·1 per cent (54) of cases. A laparoscopic CBD exploration was tried in 13·8 per cent of cases (39) and was successful in 61 per cent (24) An exclusive ES was performed in 4 per cent of cases (11). ES was performed before surgery in 85 per cent (168), after surgery in 9 per cent (18), and more recently during surgery in 6 per cent (12) according to the technique of the 'rendez-vous' in patients with a low probability of CBDS, consisting of a LC with cholangiography through cystic duct followed immediately by an intraoperative ES if CBDS was found.

Results: The mortality rate was 0·3 per cent (1), it was 0 per cent after ES and/or laparoscopy. The morbidity rate was 7 per cent (20), half of the complications linked to the surgery An ERCP was performed in 203 cases, with a feasibility rate of 97 per cent and stone founding in 60 per cent (120). An ES was performed before surgery in 183 cases (90 per cent of ERCP) with a feasibility rate of 98·5 per cent, allowing CBDS clearance in 88·5 per cent of cases (162) Morbidity after ES was 10 per cent (21) The mean hospital stay was 11 days in sequential treatment and 4·5 days in the technique of the 'rendez-vous', *vs* 20 days in cases of laparotomy after an ES or not. We noticed a marked increase in ERCP use before surgery (43 per cent in 1990–91, 71 per cent in 1992–93, 54 per cent in 1994–95), and progressively more accurate diagnosis, as shown by the decreasing rate of normal ERCP (17 per cent in 1990–93 *vs* 10 per cent since 1994) In the same way the indications for laparotomy have clearly decreased (50 per cent in 1990–91 *vs* 10 per cent since 1992).

Conclusion: Sequential treatment appears in our practice to be the standard treatment of CBDS ERCP ± ES is performed before surgery if there is a high risk of CBDS; the 'rendez-vous' procedure is planned if the risk is low, ES postoperatively is used only occasionally. We reserve the total laparoscopic treatment for (a) CBDS of large size (>1cm) of limited number (≤3) and located in a large CBD and (b) for the small stones extractable through the cystic duct. Open surgery still has a place in cases of multiple CBDS and when laparoscopy or ES are contra-indicated

Endoscopic treatment of biliary fistula: papillotomy or stenting?

Z. Wajda, M. Dobosz and A. Babicki *II Department of Surgery, Medical University of Gdańsk, 1 Prof. Kieturakis St. 80-742 Gdańsk, Poland*

The authors present 21 patients with postoperative biliary fistula. The biliary fistula was a consequence of laparoscopic cholecystectomy in six patients, open cholecystectomy in six patients, and T-tube drainage failure in four patients. In three patients the biliary leakage was recognized after right hemihepatectomy, and in two patients following stab or blunt hepatic wounds ERCP examination revealed intrahepatic bile duct leakage in five patients, while in 16 patients the bile duct injury involved extrahepatic biliary tree. The patients were divided into three groups Group 1 comprised 10 patients in whom endoscopic papillotomy was performed only, and was sufficient for fistula healing. Group 2 consisted of six patients in whom endoscopic papillotomy did not diminish biliary leakage, and consecutive endoprosthesis implacement was performed. Group 3 included five patients. In these patients endoscopic papillotomy and endoprosthesis implacement were carried out simultaneously There were no differences concerning the amount of biliary leakage and the site of the bile duct injury In all the patients the biliary fistula was healed. No complications were observed following endoscopic treatment. The mean time of fistula healing was in Group 1, 8·3 days, in Group 2 14·6 days, and in Group 3 3·9 days. As it is difficult to predict in which cases endoscopic papillotomy might be sufficient in biliary fistula healing, the authors suggest that in patients with postoperative biliary leakage, primary biliary stenting shortens hospital stay period and should be considered as a procedure of choice

Breast

Gastric metastasis of cancer of the breast

M. Alba*, E. Piedrafita*, M. Velasco*, G. Marín*,
A. Chivite de León† and L. Allende* *Department of General and Digestive Surgery, †Department of Pathology, Hospital de Sant Pau, C/. Sant Antoni Mª. Claret, 167, 08025 Barcelona, Spain

Introduction: Between 2 and 4 per cent of patients with neoplasia develop gastrointestinal metastasis. Cancer of the breast may give rise to metastasis in the digestive tract (13–27 per cent), although metastasis to bones, lung, liver or brain is more common The incidence of gastric involvement is between 3·2 per cent and 5·1 per cent. The onset of digestive symptoms in a patient with breast neoplasia may indicate metastasis.

Clinical case: A 60-year-old woman, with no significant past medical history, presented complaining of a lump in the right breast which was fixed to the chest wall, and with skin involvement in the form of 'peau d'orange'. Ductal adenocarcinoma was diagnosed on biopsy. Radionucleotide bone scanning showed metastasis to the skull, vertebral column, ribs and pelvis. Polychemotherapy was started and partial remission obtained. Treatment was continued with tamoxifen and hormone therapy Six years later, the other breast was found to be affected, and the bony metastasis had progressed, corticosteroids were given as treatment. Two months later, there was an episode of bleeding from the upper gastrointestinal tract. Thickening of the wall of the fundus and body of the stomach was seen on fibroscopy. Biopsy showed adenocarcinoma, compatible with primary breast adenocarcinoma. One month later there was a further haematemesis, with the patient dying shortly afterwards.

Discussion: Only 8·2 per cent of gastric metastasis are symptomatic, presenting with anorexia, nausea, vomiting, epigastralgia, digestive tract bleeding or dysphagia. Symptoms may appear years after the primary process. Barium meal and endoscopy show stiffening and thickening of the gastric wall, similar to that found in linitis plastica The mucosa is usually normal, and therefore biopsy may be negative. Spread is haematogenous. Costicosteroids increase the number and extent of gastroduodenal metastasis in breast cancer. Treatment may be either surgical, by radiotherapy, or by chemotherapy, depending on the extent of neoplastic spreading. Prognosis is poor.

The use of latissimus dorsi flaps in breast reconstruction after mastectomy

A.G. Alexandru University of Medicine, Plastic and Reconstructive Surgery Department, Str. Avram Iancu NR. 18, 3400 Cluj-Napoca, Romania

Breast reconstruction after radical mastectomy for cancerous or precancerous disorders may represent an imperative need, due to the physical and psychological implications for the patients. Silicone implants or prosthesis being forbidden in such cases, reconstructive treatment is confronted with special technique and strategy problems.

Techniques using muscular and musculocutaneous flaps from the rectus abdominis or the latissimus dorsi muscles allows a breast reconstruction close to the natural aspect and consistency, therefore they became a first-choice technique for the plastic surgeon.

This presentation deals with the use of the different forms of latissimus dorsi flaps: pediculated muscular flap; island muscular flap; muscular flap with complete skin island; muscular flap with skin island without epidermis We have used this method of reconstruction both after mastectomy in cancer casualties (generally followed by radionecrosis or radiodermitis) and after mastectomy in precancerous casualties, when the breast reconstruction has been usually made during the same surgical stage

We may conclude that these methods of breast reconstruction offer a high degree of satisfaction, both for the specialist (long-term postoperative results) and the patient (aesthetic and psychological result).

Therapeutic choices in local advanced breast cancer (LABC)

N. Angelescu, N. Jitea, I. Florea, T. Burcos, S. Voiculescu and G. Filipescu Coltea Hospital, Surgical Department, Bucharest, Romania

Aim: Study of the adequate schedule in the LABC.

Material and methods: In the category of LABC we included:

- tumours: T_3–T_4, multiple occupying most of the breast, invading the skin and the thoracic wall, with ulceration, oedema and satellite nodes;
- nodes: axillary (infected or fixed) and supraclavicullares distinguished clinically,
- carcinomatous mastitis without metastasis.

Therapeutic attitude in 394 patients with LABC, treated between 1984 and 1993 was established on the stage of the cancer, local aspect of the breast and general status of the patients and consisted of five schedules:

- irradiation (R0) + Surgery (S) + polychemotherapy (PCT) (124 patients);
- PCT + S + R0-PCT (100 patients);
- PCT + R0 + S (66 patients);
- S + PCT or/and R0 (55 patients);
- PCT or/and R0 (49 patients).

In almost all the patients we associated non-specific immunotherapy (NST) and hormonotherapy (HT).

Results: The postoperative morbidity consisted of wound infections (12 per cent) and local recurrence (14 per cent). *Survivors:* patients incompletely treated or not operated on died between 6 and 24 months; in the treated group there were 247 alive (65·9 per cent) at 3 years, 171 alive (45·4 per cent) at 5 years; 76 alive (23 per cent) at 7 years and 42 alive (12·3 per cent) at 10 years

Conclusions: Any patient with LABC can benefit by a complex differentiated and well organized treatment. Surgery is the 'round plate' which establishes local extension and offers enlarged potential of the adjuvant treatment.

Lymph node metastases not breast tumour response to primary chemotherapy predicts disease-free survival

C. Botti, M. Anzà, F. Cavaliere, P. Vici, F. Conti, M. Lopez and R. Cavaliere Regina Elena Cancer Institute, Viale Regine Elena 291, 00161 Rome, Italy

The aim of this study was to evaluate the independent prognostic role of surgical node staging in 69 women presenting with large but resectable carcinoma of the breast who received three cycles of preoperative anthracycline-based chemotherapy and in whom mastectomy was the conventional option. Patients who had a good clinical response to induction systemic treatment received the same chemotherapy in the adjuvant phase, while those whose response was less than optimal received alternative adjuvant chemotherapy regimens. A multivariate analysis was made to evaluate the relative influence on disease-free survival rates including clinical response to primary chemotherapy, primary pathological (p-T) staging, and the number of metastatic lymph nodes. At a median follow-up of 36 months only the number of metastatic lymph nodes was found to be an independent predictor of relapse (<0 001). Clinical and mammographic response to neoadjuvant chemotherapy as well as p-T staging did not correlate with prognosis These findings suggest that axillary dissection should be considered a fundamental step in the multimodal treatment of carcinoma of the breast in order to identify subgroups of patients with a highly unfavourable prognosis that may benefit from alternative treatments in the adjuvant setting

Partially supported by Project CNR, AIRC.

Occult *in situ* ductal carcinoma of the breast presenting with bloody nipple discharge containing malignant cells

M.J. Cardoso, A.R. Silva, I. Amendoeira, F. Pimentel, B. Bonifácio and V. Cardoso *Serviço de Cirurgia 4, Hospital de S. João, 4200 Porto, Portugal*

A 60-year-old woman presented with a 2-day history of bloody discharge from the left nipple. On clinical examination a unicanalicular bloody discharge was found but no other clinical signs were present Mammography and echography were negative, but malignant cells were present on cytological examination of the discharge. A galactography was performed and revealed a subtraction image 2 cm away from the nipple, suggesting a papillary lesion. Surgery was guided by a metal probe inserted in the bleeding duct. A 7 × 11 × 3 cm area of the gland was excised, including a fragment of skin from the nipple–areolar complex. Histology showed high-grade *in situ* ductal carcinoma, with multiple foci along a 5-cm area A second operation was subsequently performed to remove the rest of the gland together with clearance and immediate breast reconstruction. At 3 months after surgery the patient is well and recurrence-free.

High-speed biopsy of breast tumours

H. Cerwenka, M. Hoff, M. Klimpfinger, G. Rosanelli, H. Hauser and M.G. Smola *Departments of Surgery and Pathology, Karl-Franzens-University, Auenbruggerpl.29, A-8036 Graz, Austria*

Aim: To evaluate the efficiency of high-speed biopsies of potentially malignant tumours of the breast (preoperative determination of histology and receptor status as indication for neo-adjuvant therapy).
Patients and methods: In 64 female patients (mean age 56 years, range 26–81 years) high-speed biopsies were performed (system: BIP High Speed Multi 22/15 with 16-G needles at a speed of 30 m/sec hindering the tumour from slipping away)
Results: All biopsies could be used for frozen sections and for determination of receptor status Their quality was markedly improved as compared to conventional systems In 48 patients (75 per cent) malignant tumours were diagnosed, two patients had highly suspicious histology In all cases malignancy was confirmed by operation. Receptor status: negative: oestrogen receptor (ER): 33 per cent, progesterone receptor (PR): 39 per cent, both ER and PR 29 per cent Score 1–3: ER 22 per cent, PR 24 per cent Score 4–8. ER 30 per cent, PR 22 per cent. Score 9–12: ER 14 per cent, PR 14 per cent In none of the patients with benign biopsies was malignancy found afterwards. *Complications:* In one patient bleeding from a subcutaneous vein (which could be stopped by compression) was observed.
Conclusion: High-speed biopsy is a reliable and simple method for preoperative determination of histology and receptor status

Reconstruction of the shape and volume of the breast following modified subcutaneous mastectomy

G. Char, J. Lalo and J. Reynier *Department of Surgery, hospital Boucicaut 78, rue de la Convention, Paris 15ème, France*

The subcutaneous mastectomy has been criticized for unclear indications, a not fully settled technique, and disappointing results The modified subcutaneous mastectomy has been more willingly accepted because it has precise indications, the technique has been settled, and shows satisfying results. Precise indications are (a) infraclinical carcinoma (from morphometrical studies and computer information), (b) radiologically visible/microcalcifications The technique involves precise subcutaneous fat dissection, and excision of intramammary ducts at the end of operation The satisfying results include ensured recovery without recurrence both for malign disease *in situ* and for benign disease (in evolution)

Surgery was performed on 165 women. 77 per cent cancers and 23 per cent benign diseases For reconstruction a silicone prosthesis was used, but now a saline filled prosthesis is sometimes used The result was patient satisfaction in 80 per cent, reasonable satisfaction in 6·5 per cent; and not satisfied in 13·5 per cent These included four hematomas and three lymphoceles

Prognostic factors in breast carcinoma

T. Coskun, H. Kulacoglu, N.A. Kama, A. Yazgan and G. Ozdemir *Ankara Numune Hospital, 4th Department of Surgery, Ankara, Turkey*

Introduction: Today, the course of the breast carcinoma is still largely unpredictable Prognostic factors may help predict time to recurrence and overall survival rates in breast carcinoma.
Patients and methods: Between 1992 and 1995 53 patients underwent modified radical mastectomy for breast carcinoma and were followed up on for 4 years (range 3–48 months). The effect of age, number of full-term pregnancies, age at first full-term pregnancy, menopausal status, breast involved, histopathological features (skin involvement, blood vessel extension, intralymphatic extension, tumour necrosis, pattern of lymph node involvement, axillary adipose tissue involvement, Paget disease of the nipple), stage, tumour size and number of involved lymph nodes on survival were studied.
Results: Of the 53 patients, four had stage I, 26 had stage II, 22 had stage III and one had stage IV carcinoma Thirty-six (68 per cent) patients were found to have axillary lymph node involvement: nine had 1–3 and 27 had >4 positive axillary lymph nodes. Tumour diameters were ≤2 cm in four, 2–5 cm in 26, and >5 cm in 23 patients. Of the patients without positive axillary lymph nodes three had local recurrence and/or distant metastasis. One patient died of liver metastasis 18 months after the operation Of the patients with positive axillary lymph node involvement, 13 had local recurrence and/or distant metastasis. Seven patients died of their disease between 6–18 months after their operations Eight characteristics were found to have a statistically significant prognostic effect by univariate analysis: (a) age, (b) breast involved, (c) stage, (d) tumour size, (e) number of involved lymph nodes, (f) skin involvement, (g) axillary adipose tissue involvement, and (h) menopausal status When these eight characteristics were assessed by Cox's modelling, only age and axillary adipose tissue involvement were independently related to survival.
Conclusion: The results of this study have shown that age and axillary adipose tissue involvement independently affected overall survival so that patients younger than 40 years old and with axillary involvement had a poor survival.

Male breast cancer: our experience

A. Sierra García, M.E. Pertejo Muñoz, F. Fernández Ferrero, E. Garrote Nieto, A. García Muñoz Nájar, G. Pérez Mangas, M. Quadros Borrajos and C. Fernández Monge *Hospital Universitario 12 de Octubre, Carretera de Andalucía, Km 5400 28041 Madrid, Spain*

The complete material of male breast cancer, 76 cases, is described and analysed concerning different parameters The mean age at diagnosis was 61·32 years. Breast cancer in close relatives, smoking, alcohol intake, diabetes and tuberculosis, were considered as risk factors The right breast was affected in 64·47 per cent of the cases. The most frequent symptoms were tumour (93 per cent), pain (45 per cent), axillary adenopathies (39 per cent), retraction (30 per cent). Age at diagnosis, axillary lymph node status and tumour size all had significant prognostic importance, with axillary lymph node status as the strongest factor

Treatment of each patient was individualized Therapy included surgery (3 per cent), radiation therapy (7 per cent), hormonotherapy (3 per cent) as single modalities, or in combination surgery-HT (1 per cent), RT-CHT

(2 per cent) The histopathology (invasive ductal *c.* 89 per cent), distribution of TNM classification (Stage III 48 per cent), local recurrence (28 per cent), and metastasis (55 per cent) were analysed. The overall mortality was 55 per cent of the patients, alive free from disease (42 per cent), and 8 per cent were alive with recurrence.

Conclusions: Incidence is greater in smokers and drinkers. There is a bilateral and familiar predisposition. We have found an advantage when gynaecomastia and neoplasm are associated A worse prognosis is given by tissue invasion and lymphatic diffusion.

Contrast MRI in the management of suspected local recurrence after conservation therapy for breast cancer

P. Giordano*, K. Pointon†, B. Murtuza*, W. Gedroyc† and M. Ghilchik* **Academic Surgical Unit and †Department of Imaging, St Mary's Hospital Medical School, London W2, UK*

The detection of local recurrence after conservative surgery and radiotherapy is often a diagnostic dilemma. Magnetic Resonance Imaging (MRI) with gadolinium enhancement is a new and potentially useful investigation. We present our findings of 31 MRI examinations performed during follow up in 26 patients (average age 55·5 years, range 39–74 years) who had previously undergone conservative treatment for breast cancer. The indication for MRI was suspected local recurrence on clinical or radiological grounds, without a definitive diagnosis. The examination was carried out with 1·5T IGE Sigma Advantage System using a Fast Multiplaner Spoiled Grass sequence with chemically saturation pre- and post-20ml Gadolinium DTPA boluses. The mean interval between surgery and MRI was 47 months (range 16 months–10 years).

True positive is considered an early enhancement confirmed by a positive postoperative histology. True negative is defined as a combination of a no enhancement on MRI report, along with no clinical or mammographic changes during the subsequent 12-month follow-up. Results (*n*) are shown in Table 1.

MRI	True +	True −	False +	False −	Sensitivity	Specificity
31	11	18	1	1	91·6 per cent	93·5 per cent

Furthermore, in 13 patients (50 per cent), MRI directly influenced management: in four patients MRI led to the surgical excision of an impalpable lesion not seen on mammography. In a further nine patients with highly suspicious mammography, negative MRI avoided a needless intervention.

MRI is a useful tool in the assessment of the difficult post-surgical and post-radiotherapy breast, and in selected patients has proved to be cost-effective in this respect.

Ductal adenoma of the breast: a clinical problem still to be solved

A.V. Granai, A. Manno, L. Giacomelli, R. Gabatel, G. Fabrizio, R. Finizio, E. Gagliarducci, C. Porcelli, E. Gallinacci, L. Minocchi and A. Pulcini *VI Surgical Department, Rome University 'La Sapienza', Viale Regina Elena, 324, 00161 Rome, Italy*

The authors report their experience about a case of ductal adenoma of the breast with the aim of giving their contribution to the present debate about the morphological and immunohistochemical features and the biological potential of this lesion.

A 27-year-old woman with previous diagnosis of benign intraduct papillary lesion presented to us with a 1·5cm lump in the upper outer quadrant of the right breast and nipple discharge but no palpable lymph nodes in the axilla Ultrasound and mammography give no specific picture, cytological features of the nipple discharge were unremarkable and tumour markers were negative. Tumorectomy was performed but histological examination of the specimen on frozen section was not helpful in clarifying the exact nature of the lesion. The histological examination on paraffin sections, cut at 5μm and stained with Em/Eos, showed multiple nodules in which glandular tubules were separated by dense and abundant fibrous stroma and newly formed elastic fibres. The tubules were lined by luminal epithelium and basal myoepithelium Glandular structures were often distorted by sclerosing phenomena thus showing worrying, pseudo-infiltrative aspects. A stellate central scar, as well as pictures of apocrine metaplasia, were also present. All these elements led us to characterize the lesion as 'multiple adenomas of the breast'. A range of antibodies were used immunocytochemically to characterize the phenotype of the lesion with the following results: positive reaction to polyclonal anti-keratin antibody MNF116, polyclonal Anti-Smooth Muscle Antibody (ASMA) and antibody against c-erbB2 protein; negative reaction to anti-type IV collagene monoclonal antibody at the level of the basement membrane around the epithelial island and anti *p53* protein; low proliferating rate (Ki 67); intranuclear positivity to antibodies anti-progesterone receptors (PR-ICA) in 60 per cent of cells and to antibodies anti-oestrogen receptors (ER-ICA) in 53 per cent of cells (both made on frozen section).

The typical pseudoinfiltrative aspect of the ductal adenoma of the breast can easily mimic carcinoma, especially on frozen section. The pathologist should therefore take care of some peculiar histological features which clearly identify the benign nature of the lesion, such as presence of the myoepithelial layer surrounding the epithelial tubules, integrity of the basal membrane, picture of apocrine metaplasia, low proliferating activity. Immunohistochemistry can be useful in clarifying the presence of such aspects but in our experience the results have been contradictory. In fact, although reaction against ASMA and cytocheratines demonstrated the presence of the myoepithelial layer, staining with anti-type IV collagene showed the absence of the basement membrane. The overexpression of the c-erbB2 protein, which can be a sign of the early phase of the neoplastic transformation and the positivity to PR-ICA and ER-ICA, sign of susceptibility of the mammalian epithelium to proliferating stimuli, has been also found. On the other hand Ki 67 staining showed a low proliferating rate and *p53* staining was negative.

We think it advisable to suggest a wide use of immunohistochemical typing of these lesions to confirm in larger series our results and thus clarifying the real nature of the ductal adenoma of the breast.

Subcutaneous mastectomy for benign disease

A. Güemes, B. Delgado, J.M. Miguelena, I. Gil, R. Palacín, F. Burdio and J. Torcal *Department of Surgery, Hospital Clínico Universitario, Av. San Juan Bosco 15, Zaragoza, Spain*

Fibrocystic disease (FD) is a benign condition of the breast that occurs in 40 per cent of women. Mammography, ultrasound examination, fine-needle aspiration (FNA) or even open biopsy is advocated for disclosing any malignancies in those patients. Subcutaneous mastectomy with reconstruction is not usually indicated as FD is not a premalignant condition but in selected cases, such as those having gigantomastia, cancerophobia, mamalgia or even patients undergoing multiple Rx or FNA examinations, surgical excision should be the treatment of choice.

Aim: To present the results of subcutaneous mastectomy with reconstruction for benign disease at our institution.

Patients and methods: We present our series of 65 patients with benign disease of the breast treated with subcutaneous mastectomy during the last 6 years. Selection criteria were: patients with three or more FNA or open biopsies in the last two years, multiple fibroadenomas, fibrotic breasts unable to recognize any lesion, cancerophobia, giant fibroadenomas and other benign tumours. The surgical technique used was a subcutaneous mastectomy, leaving a small portion of mammary tissue below the areola, to preserve irrigation of the nipple areola complex (NAC). Reconstruction was made using the fat and de-epithelialized skin, in pendulous breast, or using prosthesis in case of small breasts.

Results: Sixty-five patients were treated, ages ranged between 14 and 60 years old. Multiple FNA was the major indication (50 per cent) followed by fibrotic breasts (29 per cent) and multiple fibroadenomas (10 per cent).

Eight cases were reconstructed using prothesis and the rest using her own fat and skin tissue Local complications were present in 12 cases, the most common was NAC necrosis (10 cases), which needed reconstruction (grafting) in all cases One patient suffered a breast abscess and other a haemorrhagic effusion that needed reintervention Pathological examination of the specimens showed benign conditions in all but one case of *in situ* ductal carcinoma. Satisfactory results, after the operation, were achieved in all but the case of mammary abscess

Comments: Subcutaneous mastectomy and reconstruction has a role in the treatment of benign diseases of the breast and can be easily performed by general surgeons. The high rate of complications should be avoided as we become confident with techniques of plastic surgery

Axillary lymph node dissection in non-palpable early breast cancer: when can it be avoided?

P. Kauffmann, G Le Bouedec, C. Pomel, V. Feillel, M. de Latour and J. Dauplat *Centre Régional de Lutte Contre le Cancer Jean Perrin 58, rue Montalembert, B.P. 392, 63011 Clermont-Ferrand Cedex, France*

Axillary node management for non-palpable early breast cancer is one of the topics of the day Thus, we report a study including 265 axillary node dissections performed from January 1982 to February 1995. All node dissections were performed for mammographically detected early breast cancers The mean age of patients was 57 years (32–74 years). Lesions were divided into· 36 ductal carcinomas *in situ* (DCIS), 23 microinvasive carcinomas, 206 invasive carcinomas. The 206 invasive carcinomas were categorized in 179 invasive ductal cancers (IDC), 25 invasive lobular cancers (ILC) and two mucinous invasive carcinomas.

The sizes of histological invasive component were divided into ≤5 mm 38 cases; 6–10 mm 84 cases, 11–15 mm 53 cases; 16–20 mm 16 cases; >20 mm 15 cases Axillary dissection was immediately performed during initial surgical procedure in 209 instances (78·9 per cent) and in second intention for 56 patients (21·1 per cent)

Nodal positivity for DCIS, microinvasive carcinomas or invasive carcinomas ≤5 mm was 0/97 (0 per cent) The overall positivity for invasive carcinomas was 16/206 (7·8 per cent) For invasive carcinomas larger than 5 mm, the overall positivity was 16/168 (9·5 per cent) divided in 9/84 (10·7 per cent) for tumours >10 mm and 7/84 (8·3 per cent) for tumours measuring 6–10 mm Consideration should be given to eliminating axillary node dissection for DCIS, microinvasive and invasive breast tumours measuring 5 mm or less because of the lack of positive nodes in this study

With the availability and the development of prognostic indicators, routine lymph node dissection can thus be avoided for small non-palpable early breast cancers, saving patients an additional morbidity.

Early breast cancer: is surgery enough?

I. Lorent, D. Hertens, I Veys, D. Noterman and J -M. Nogaret *Jules Bordet Institute, Department of Surgery, rue Héger-Bordet, 1, 1000 Brussels, Belgium*

With a retrospective analysis, we evaluated the results of our treatment approach for infraclinical breast cancers Seventy-three women with a small breast cancer were seen in our department between January 1987 and December 1991. Patients' ages ranged from 35 to 79 years with a mean of 55 years of age Eight patients were previously treated for a contralateral breast neoplasm (seven invasive cancers and one DCIS). In all cases, mammography was positive 60 per cent of the tumours were identified as microcalcifications Ultrasound was performed in only 16·4 per cent of the patients, revealing an abnormality, suggestive for cancer, in 41·7 per cent Of the patients 30 per cent had a preoperative fine-needle aspiration The results were suggestive or positive for tumour in 50 per cent

Harpoon marking preoperatively permitted localization and extraction of all lesions without significant difficulties. Breast conservative surgery was performed in 84 per cent of the patients No postoperative complications were encountered. The pathology reports concluded for 32·9 per cent of DCIS and 67·1 per cent of invasive cancers. Forty patients received adjuvant radiotherapy, five had adjuvant chemotherapy. The mean follow-up of this group is 5 years Ten recurrences were diagnosed in nine patients, half of them developing in the same quadrant as the initial surgery: 90 per cent of these had no clinical expression. These relapses were present in seven patients treated by simple tumorectomy. Recurrences appeared in 25 per cent of the initial DCIS and in 8 per cent of the initial invasive tumours No distant dissemination occurred The addition of radiotherapy to surgery in our analysis diminished the appearance of local relapses.

However, simple surgery does not seem to affect overall survival Future prospective randomized studies will probably permit to estimate the place of adjuvant radiotherapy for infraclinical screen detected cancers.

Postmastectomy morbidity in Stage IIIB breast cancer patients who have had preoperative chemotherapy

C. Ozaslan, N. Karaman, A. Güngor, S. Çelebioğlu, A.F. Ayhan and M. Altınok *Ankara Oncology Hospital, Ankara, Turkey*

Postoperative morbidity of preoperative chemotherapy plus radical mastectomy and radical mastectomy alone groups were compared.

Twenty-five patients with Stage IIIB breast cancer were given preoperative chemotherapy and after clinical regression they had radical mastectomy (Group 1). In the other group 42 patients with Stage IIB breast cancer (Group 2) had radical mastectomy. Postoperative morbidity was compared between these two groups Group 1 patients were given 2–4 cycles of chemotherapy and after clinical regression, operated within 15–20 days after the last chemotherapy cycle.

Seroma formation was seen in 20 per cent of patients in the first group; and 19 per cent in the second group ($P > 0{\cdot}05$). Wound necrosis rates are not different in the preoperative chemotherapy group compared with the radical mastectomy alone group (32 per cent and 21 per cent, respectively, $P > 0{\cdot}05$) The incidence of wound infection is similar for both groups (12 per cent and 11 per cent respectively, $P > 0{\cdot}05$).

This study provides evidence that preoperative chemotherapy and radical mastectomy can be performed without increased morbidity

Axillary recurrence in patients undergoing surgery for cancer of the breast

L. Ocaña, M. Molina, C. Soler, E. Alba, R. Ruiz, J. Verdugo, R. Mazure and M. Dominguez *Breast Unit, Service of Surgery A, University Clinic Hospital of Malaga, Malaga, Spain*

In twelve years the Breast Unit of our hospital has surgically treated more than 1700 patients, 1259 of them because of a neoplasic pathology We followed a combined multidisciplinary study and treatment which included radical surgery of the breast, and more common today, conservative treatment, even with an axillary dissection, installation of metal guide wires for localizing non-palpable lesions, adjuvant treatment and reparative surgery post-mastectomy.

Of all the patients with a malignant pathology, 405 (including five males) suffered some kind of recurrence, local or metastatic In 21 cases we found a local axillary recurrence, 5·18 per cent of the total of recurrences and 1·66 per cent of the total of carcinomas treated, and of the total of dissections practised

Two of the axillary recurrences were in men The median age was about 50 years old The median size of the tumour was between 2 to 5 cm For subsequent adjuvant treatment, seven needed radiotherapy, four chemotherapy, two hormonal therapy

In conclusion we emphasize the importance of a complete axillary dissection to avoid recurrence The incidence of recurrence is greater in tumours larger than 2 cm. We stress the importance of the adjuvant treatment and its potential to avoid axillary recurrence

Needle localization and biopsy (stereotaxis) of non-palpable lesions in breast cancer

B. Perez, D. Gaitan, A. Bosquet*, F. Ardoy*, F. Luque, L. Vazquez, P. Torne and J.M. Garcia *Hospital Universitario San Cecilio, Avenida Dr Oloriz 16, 18012 Granada, Spain*

Aim: To determine the percentage of malignant non-palpable breast lesions detected by stereotaxis.

Patients and methods: A total of 114 biopsies was performed, introducing a guide wire into the lesion under radiological control (mammography): Once the guide wire is positioned by the radiologist, the biopsy is performed in the operating theatre and the biopsy specimen is sent to the mammography department for radiological confirmation of the presence of the suspicious area Selection criteria: (a) mammographical findings: architectural alterations, asymmetrical density, non-palpable node and microcalcifications; (b) Dubois fine-needle breast biopsy.

Results: Radiological confirmation of the biopsy specimens and a pathological study gave the following results: benign lesions: 54 (47 per cent), normal parenchyma· 15 (13 per cent); malignant and parenchymal lesions: 33 (29 per cent); high risk lesions: 12 (10 per cent).

Conclusions: Stereotaxis or wire-guided biopsy is a safe and effective procedure for early detection of breast cancer. Close collaboration between the surgical and radiological departments is required. Specimen resection is facilitated, surgical intervention is minimized and hospital days are reduced

Problems of diagnosis and treatment in phyllodes tumours of the breast

G.D. Subţirelu, R. Duţu and I. Bălănescu *Bucharest Institute of Oncology, SOS Fundeni 252, Sector 2, 72425 Bucharest, Romania*

Phyllodes tumour is an uncommon neoplasm of the breast. A retrospective review of 91 patients with phyllodes tumours of the breast (PTB) was performed to evaluate if clinico-pathological and histological markers taken into account correlated with clinical behaviour, and to determine the influence of the extent of the operation performed on clinical outcome

All patients were females. Their ages ranged between 12 and 67 years with a median of 40 years. They have been operated in Bucharest Institute of Oncology between 1974 and 1990 Using histological criteria PTB were classified in benign (B), borderline (BL) and malignant (M). The surgical treatment performed for BPTB (79 patients) was local excision (LE), 49 [five recurrences (R)], extended local excision (ELE) 12 (five R), mastectomy (MA) 16 (one R), tumorectomy two. The recurrences were six benign (noted at 3–98 months with a median of 45·8 months) and five malignant (at 3–29 months with a median of 14·8 months). For the MPTB the treatment was LE in three cases (with two R at 15 and 44 months with a median of 29·5 months) and MA in nine patients (no R).

The ongoing study upon the cases with recurrent tumours showed us that there are no clinical or histopathological criteria to predict the benign or malignant outcome of the PTB In regard to the surgical treatment the only way of avoiding recurrences is tumour excision with 2-cm safety-border of healthy tissue for BPTB and mastectomy (simple or complex) for MPTB or for the voluminous BPTB

Stereotactic surgery of non-palpable breast lesions: an analysis on 100 cases

R. Tersigni, R. Mencacci, L. Alessandroni, M. Sessa and T. Scala *Departments of Surgery and Radiology, Nuovo Regina Margherita Hospital, Rome, and Santa Maria Goretti Hospital, Latina, Italy*

A suspicious non-palpable breast lesion, detected with routine or screening mammography, can be easily managed using a stereotactic radiological localization. In the case of confirmed malignant lesion, and in absence of multicentricity, conservative therapeutic protocols can be adopted with good prognosis.

From 1988 to 1995 we performed 100 operations for suspicious non-palpable breast lesions, represented by clusters of microcalcifications, density lesions (masses, architectural disruptions and asymmetries) and mixed lesions. The localization of the lesion is obtained by a bidimensional mammographic technique, using a curved J metallic wire as a guidance for a wide excisional biopsy Specimen radiograph must be done to confirm adequacy of the biopsy; intraoperative histological examination is required to assess adequacy of margins in case of cancer Prior to fixation some material is to be retrieved for hormone receptor assays.

Overall incidence of malignancy was 22 per cent: nine (36 per cent) intraductal cancers (median size 0·5 cm), 10 (41 per cent) infiltrating ductal cancers (median size 1 cm); two (9 per cent) lobular infiltrating cancers and one (4 per cent) mucinous cancer. Of the lesions 83 per cent were less than 1 cm in main diameter; in three cases a multicentric neoplasm was found. Tumour stages were 4 TisNx, 11 T1N0 and 7 T1N1 The operations performed were wide lumpectomy in four cases (18 per cent), wide lumpectomy with axillary dissection in 10 cases (45 per cent) and modified radical mastectomy eight cases (36 per cent). After a median follow-up of 37 months no cancer relapse was detected.

Early breast cancer detection with localization biopsy of impalpable breast lesions

E. Tzoracolefhterakis, J. Maroulis, K. Vassiou, A. Kapetanopoulou and C.D. Scopa *Department of Surgery, University of Patras, Patras, Greece*

Localization biopsy for impalpable breast lesions imaged by mammography is a means of accurately excising the suspicious lesions and avoiding an unnecessarily large biopsy.

In the last 5 years, 63 women underwent a needle localization breast biopsy (NLBB) for impalpable breast lesions. The median age was 49·6 years (range 33–66 years). Only three of them were elderly (>65 years old). The Kopans localization needle and hookwire was applied in all instances with the aid of a special mammographic grid.

The application of the method yielded a total of 11 breast cancers (17·4 per cent). The final staging of the patients found to have a breast cancer was. two Stage I, two Stage IIA, one Stage IIB, two Stage IIIA, one Stage V, two lobular *in situ* and one ductal *in situ* carcinomas. Four underwent conservative surgery and another four total mastectomy with standard axillary dissection. The *in situ* carcinomas were treated with simple mastectomy.

It is concluded that needle localization biopsy for suspicious impalpable breast lesions yields a high percentage (17·4 per cent) of breast cancers This is in accordance with other previous series with a quoted American national average of 15 per cent

Colorectal

Caecal tumour mass: differential diagnosis between solitary caecal ulcer and caecal carcinoma

D. Agoli, N. Naumov, D. Smileski, G. Sukovic, I. Mostrov, K. Trpenovski and L.J. Ivkovski *Medical Center, Ohrid, Macedonia*

Introduction: Solitary caecal ulcer (SCU), is a rare, benign disease, intraoperatively diagnosed in operations performed upon acute appendicitis in over 90 per cent of cases. Macroscopically, it is a peptic caecal ulcer on the antimesenteric border, penetrating the parietal peritoneum, badly demarcated from the surrounding tissue, resembling an ulcerated caecal carcinoma. Microscopically, a mucosal and submucosal ulcer, without any atypical and malignant cells is found. Therapy ranges from conservative to radical right hemicolectomy.

Aim: To present a patient with solitary caecal ulcer, who was radically treated because of malignancy suspicion.

Results: A 28-year-old patient was operated upon for acute appendicitis. During the operation, a quiet appendix and caecal tumour mass penetrating the surrounding tissues, highly suspected for malignancy, was found. After the exploratory laparotomy, an irrigography, ultrasound and laboratory investigations were done, during the preparations for radical operation. Right radical hemicolectomy was performed a week later. On histopathological investigation a benign caecal ulcer was detected by microscopy.

Conclusion: Solitary caecal ulcer could be a great differential diagnostic problem, in contrast to caecal cancer. Although it is a self-limited disease, a radical right hemicolectomy is performed very often. In any operation performed because of acute appendicitis, where a caecal tumour mass is intraoperatively detected, it could be a benign solitary ulcer.

Local recurrence of rectal cancer: our experience

M. Agresti, M. Desantis, P. Falco, A. Ferraro, V. Colella, G. Moccia, G. Romano and L. Coscia *Cattedra di Chirurgia Generale, Seconda Universita, Piazza Miraglia 5, Napoli, Italy*

In rectal cancer surgery anastomotic or pelvic local recurrence predominantly affects the morbidity and mortality of this treatment, although it is possible to overcome manual resection technical limits by using staplers.

The survival for this pathology, found in the literature, ranges between 18 and 63 per cent within 5 years. From a statistical point of view, this improved during the 1970s, although subsequently it levelled. This is probably due to the unsuccessful resolution of aetiopathogenetic, diagnostic and therapeutic problems of colorectal cancer. However, attention is now directed to the identification of those clinical, histopathological and surgical aspects, mostly important for prognoses. Many criteria are to be taken into account in local recurrences prevention after rectal cancer treatment, not forgetting radical surgery with a 2 cm limit from the tumour, associated with lymphadenectomy up to the third level.

In the last 50 years, the most important classification of colorectal cancers can be surely considered to be Dukes, although there has been modification in order to increase prognostic capacity, paying more attention to lesion depth, location and lymphonodus metastases.

Data concern a group of 50 patients out of 78 from the Institute, selected on the basis of the future possibility of carrying out checks (tumour markers, endoscopic and biopsy checks, radiological and clinical examinations), and who had undergone surgical operations for sigma-rectal cancer from 1 January 1991 to April 1996. Sixty-three operations have been performed: 34 anterior resections (54 per cent); nine abdominoperineal resections according to Miles (14·2 per cent); 13 resections according to Hartmann (20·6 per cent); two local excisions (3·2 per cent), three for complications (4·8 per cent), two explorative laparotomies (3·2 per cent). Of these 63 operations, nine were performed for local recurrences (14·3 per cent). Among these, no recurrence has been observed in the seven patients treated in 1991. In 1992, two recurrences (22·2 per cent) in one patient only (Dukes B) have been observed, the first after anterior resection, the second after abdominoperineal resection according to Miles. Four (44·4 per cent) have been observed in 1993, two after anterior resection (Dukes C) and two in one patient only (Dukes B) after anterior resection and a Hartmann's resection. In 1994, one (11·1 per cent) has been observed after local excision (Dukes A) and two (22·2 per cent) have been observed in 1995, one after local excision (Dukes A) and one after anterior resection (Dukes A). According to the classification of Dukes, we could identify nine patients at A stage (18 per cent), 13 at B stage (26 per cent), 18 at C stage (36 per cent) and 10 at D stage (20 per cent). The total survival rate has been 56 per cent (28 patients).

On the basis of data taken from literature analysis and our case records, even if retrospective data are not significant with regard to the short period considered, we may preliminarily conclude that Dukes classification for distal rectal cancer is not always consistent with prognosis, prognosis is not completely consistent when lymph nodes are involved, intraoperative valuation is really very important. Then it brings about the most efficient therapeutic choice, although it cannot be easily and commonly standardized, being subjective to each surgeon. In fact, afterwards, the treatment often looks inadequate in comparison with cancer development, compared to when predicting parameters are taken into consideration.

Does diverting colostomy increase recurrences in colorectal cancer?

D. Huerga Alvarez, A. Navarro Pomares, A. Badía de Yébenes, A. Payno de Orive, J.L. Souto, S. Rivas Fernández and R. González-Cajigal *Fundación Jiménez Díaz, Clínica de La Concepcion, Universidad Autónoma de Madrid, Avda. Reyes Católicos 2, 28040 Madrid, Spain*

Experimental studies suggest that carcinogenesis at colorectal anastomosis is inhibited by proximal defunctioning stoma and promoted by the closure of it. We have studied the relevance of these findings in the disease-free time and in the prevalence of tumour recurrence, in a prospective study over a selected group of all the patients surgically treated for colorectal adenocarcinoma between 1991 and 1995 (417 total), excluding D Dukes stage, those older than 80 years, palliative resections and postoperative deaths (within 1 month). Only left and sigmoid colon and rectal tumours were included, except those where abdomino-perineal amputation was performed. A final group of 144 patients (study population) was divided in two groups: those without colostomy (Group A = 102), and those in whom a temporary stoma was fashioned (Group B = 42). The last divided also into lateral colostomy with primary anastomosis (B1 = 21) and end colostomy (Hartmann's procedure), B2 = 21. The overall follow-up has been of 125 cases (73 per cent), 93 in Group A, 19 in B1 and 13 in B2. Groups B and B1 have been compared independently with A (control group). Comparisons were done using χ^2 analysis and Fisher's test, Gauss distribution, or Mann–Whitney test; 1-year disease-free survival rate with Kaplan–Meier method and comparisons with log rank test.

The global free-disease mean time was 11·9 (±2·7 $P < 0{\cdot}05$) months without significant difference between Groups A and B or A and B1, but the 1-year free-disease rate was 72 per cent in Group A, 43 per cent in Group B1 and 46 per cent in Group B2 ($P = 0{\cdot}00003$ and $P = 0{\cdot}001$ between A and B1, and A and B2, respectively). The prevalence of recurrences is also higher in Group B (19/32 = 59 per cent) and in Group B1 (11/19 = 58 per cent) than in Group A (21/93 = 23 per cent) (both $P < 0{\cdot}01$)

No differences were found between Group A and B in age (67·5–68·9), sex (male/female = 56/46 and 25/17; respectively), tumour site, Dukes stage, number of adenopathies isolated or tumoural markers. Statistical difference was found in the relationship between elective and emergency surgery (96/6 in Group A, 24/18 in Group B, $P < 0{\cdot}001$), but if an elective surgery group is compared alone, there is still more recurrence in Group B (11/19 = 58 per cent) than in A (19/87 = 22 per cent) ($P < 0{\cdot}01$).

No significant differences were found between Group A and B1 in age, sex, Dukes stage, number of adenopathies isolated or tumoural markers, and anastomotic dehiscence (4/102 = 4 per cent and 2/21 = 10 per cent, $P = 0{\cdot}384$) Statistical difference was found in the relationship between neoplasm location (left colon/rectum = 65/37 in Group A and 4/17 in Group B1, $P = 0\ 0002$; elective and emergency surgery (96/6 in Group A, 18/3 in Group B1 $P < 0{\cdot}001$; and distal resection margin (<2cm/>2cm = 18/84 in Group A and 10/11 in Group B1) If those items are individualized a relationship between prevalence of neoplasm recurrence and lateral colostomy cannot be proved in rectal tumours, even it is rather elevated in the study (50 per cent *vs* 26 per cent, $P = 0{\cdot}187$). If elective surgery is compared alone, higher prevalence of recurrence in Group B1 is seen (8/16 = 50 per cent *vs* 19/87 = 22 per cent; $P = 0{\cdot}004$). In the group of resections with unaffected margin >2cm prevalence of tumoural recurrence is lower in patients with no lateral colostomy (14/70 = 20 per cent) than in those of Group B1 (5/9 = 56 per cent) ($P = 0{\cdot}0325$).

Conclusions: Temporary faecal diversion increases prevalence of local recurrence and decreases 1-year free-disease survival rate, independently of Dukes stage, neoplasm site, timing of resection, and free distal margin.

Emergency subtotal/total colectomy with anastomosis for acutely obstructed carcinoma of the left colon

J.P. Arnaud, R. Bergamaschi, G. Becouarn and
C. Casa *Department of Visceral Surgery, CHU Angers, Angers 49100, France*

Aim: The operation of choice for acutely obstructed carcinoma of the left colon is controversial. The aim of the study was to evaluate the results of its management by emergency subtotal/total colectomy with immediate anastomosis without diversion.

Methods: An emergency subtotal/total colectomy was performed in 44 patients (mean age 72·4 years). Inclusion criteria were reasonable operative risk, resectable acutely obstructed carcinoma, massively distended colon of dubious viability and likely to contain ischaemic lesions, signs of impending caecal perforation, and masses suggesting synchronous colonic cancers

Results: Postoperative mortality was 6·8 per cent. Two patients over 90 years of age died postoperatively as result of cardiopulmonary complications. An 83-year-old female died as a result of an anastomosis dehiscence. Morbidity was 6·8 per cent including one fistula which recovered without surgery There were three synchronous colon cancers. Six months after surgery, the mean daily stool frequency was two following subtotal colectomy and three after total colectomy.

Conclusion: Emergency subtotal colectomy achieves, in one stage, relief of bowel obstruction and tumour resection by encompassing a massively distended and faecal-loaded colon with ischaemic lesions and serosal tears on the caecum, ensures restoration of gut contiguity via a 'safe' ileocolonic anastomosis, and removes occasional lesions proximal to the index cancer It is a safe procedure given that operative mortality rates are as low as with elective surgery.

Mutations of mismatch repair genes in sporadic colorectal cancer

M. Moreno Azcoita, C.L. Maillo, R. Vazquez, P. Artuñedo,
F. Angulo, M.A. Fernández-Peralta and J.J. González-Aguilera *Servicio de Cirugía General, Hospital Universitario Getafe, Ctra Toledo Madrid, Departamento de Genética, Facultad de Biología, UAM, Madrid, Spain*

Mismatch repair genes are implicated in the aetiology of hereditary non-polyposis colorectal cancer The alteration of these genes can be detected when microsatellites are studied, because of a phenomenon of replication errors (RER+ phenotype) that produces microsatellite instability (MIN) Although mismatch repair genes are well known in hereditary colorectal cancer (CRC) their role in sporadic CRC is not established. We have performed a study in a sample of sporadic CRC with the aim of determining the implications of mutations of mismatch repair genes in these tumours.

Patients and methods: Ninety-six sporadic CRC treated from February 1992 to December 1993 have been studied. The samples obtained from fresh tissues have been normal mucosa and tumour, and blood from peripheral blood. Five microsatellites have been amplified by PCR: AFM093xh3 (chromosome 2p), Mfd27 (chr 5q), TP53 and Mfd152 (chr 17p) and SE289 (chr 18q). PCR products were electrophoresed in acrylamide gels. RER+ phenotype has been related to some clinicopathological variables· age, sex, location of the tumour, level of differentiation and Dukes stage Statistical analysis has been carried out by χ^2 and Student's *t*-tests.

Results: Thirty-seven (38·54 per cent) tumours presented MIN, 22 males and 15 females. The results according to the variables are represented in Table 1.

		Location		Level of differentiation			Dukes Stage			
	Age	Right	Left	Well	Moder	Poor	A	B	C	D
RER+	67 4	13	24	18	17	1	3	13	13	8
RER−	69	9	48	35	17	1	6	24	20	5
Total	68 4	22	72	53	34	2	9	37	33	13

Although there is no difference according to the age, 100 per cent of patients <47 had RER+ tumours MIN appears in right-sided tumours with a statistical significant difference. There is a tendency of RER+ tumours to be undifferentiated. MIN is present from the first stages of CRC as is represented in Table 2

Dukes Stage	Percentage
A	33·33
B	35·13
C	39 39
D	61 53

Conclusions: MIN is present from the first steps of sporadic CRC tumorigenesis indicating that mismatch repair genes could be responsible for a percentage of sporadic cancers. Those sporadic tumours with RER+ phenotype share characteristics with HNPCC tumours which could mean that this genetic alteration may determine a specific tumour behaviour and prognosis.

Extended right hemicolectomy in the treatment of large bowel obstructions

Á. Balogh, I. Zöllei and G. Lázár *Department of Surgery A, Szent-Györgyi Medical University, Szeged, Hungary*

Eighteen extended right hemicolectomies were performed for the treatment of large bowel obstructions caused by cancers of the transverse colon (six patients), of the splenic flexure (eight patients) and of the descending colon (four patients). A primary ileocolic anastomosis was made in each case. The mean age of our patients was 66 years with 10 older than 70 years. We used a special method for the intraoperative decompression of the distended bowels orally from the obstruction. Nine ileocolostomies were made by one layer manual suture and nine were stapled. No anastomotic leakage occurred. One patient died due to cardiorespiratory failure Six septic complications occurred. Four wound infections required a major reoperation Two patients had sterile disruptions of the laparotomy wound On the basis of our results the extended right hemicolectomy with intraoperative decompression of the bowels and primary ileocolostomy is a safe method in the treatment of large bowel obstructions. The procedure is oncologically radical, prevents the intraoperative contamination, and reconstructs the gastrointestinal tract in a single intervention

Prospective comparison of laparoscopic and conventional colorectal surgery for cancer: lymph nodes and margins

C. Barrat, R. Turner, N. Rizk and G. Champault *Hospital Jean Verdier, Department of Surgery, Av du 14 Juillet, 93140 Bondy, France*

We report a prospective non-randomized study of margins and lymph nodes comparing purely laparoscopic resection (PL) (n = 12), laparoscopically-assisted resection (LA) (n = 16), and conventional laparotomy (CL) (n = 23) for colorectal carcinoma

Patients and methods: In Group 1 (PL, n = 12) there were seven sigmoid carcinomas and five rectal carcinomas. The procedures performed were· low anterior resection (5), sigmoid colectomy (5) and left hemi-colectomy (2) In Group 2 (LA, n = 16) there were six ascending colon carcinomas, five rectal carcinomas, three sigmoid carcinomas and two descending colon carcinomas The procedures performed were· right hemi-colectomy (6), low anterior resection (4), left hemi-colectomy (3), sigmoid colectomy (2), and abdomino-perineal resection (1). In Group 3 (CL, n = 23) there were eight rectal carcinomas, six ascending colon carcinomas, five sigmoid carcinomas, four descending colon carcinomas The procedures performed were. right hemi-colectomy (6), low anterior resection (5), sigmoid resection (5), left hemi-colectomy (4), abdomino-perineal resection (3)

Results: The results are shown in Table 1 as median values (range)

	G1 (PL) (n = 12)		G2 (LA) (n = 16)		G3 (CL) (n = 23)	
No. of nodes resected	6·5	(1–19)	6·3	(0–18)	7·3	(0–18)
Length of bowel resected	14·3	(7–21)	21·6	(6–29)	24·3	(9–45)
Distal resection margin (cm)	4·1	(1·5–7·5)	8·4	(1·5–17)	6·6	(1·5–20)

There were no significant differences between the three groups with respect to the number of nodes resected There were however significant differences between Group 1 and Groups 2 and 3 for the total length of resection as well as the length of the distal margin

Conclusions: This small study serves to highlight differences in the oncological aspects of colorectal cancer surgery. We believe that laparoscopic resection of colorectal malignancies should be undertaken only as part of a prospective randomized trial.

Is there a genetic defect in the metabolism of butyrate in ulcerative colitis patients?

F. Bianco, D.G. Corry, D.M. Lewis, M F Grahn and N.S Williams *Academic Surgical Unit, Royal London Hospital, Whitechapel, London E1, UK*

Because the metabolism of butyrate is impaired in colonic mucosa isolated from patients with quiescent ulcerative colitis, our aim was to find out whether this results from a genetic defect In order to evaluate this hypothesis the oxidation of butyrate in extra-gastrointestinal cells was tested We analysed lymphocytes and granulocytes in a control group of 13 patients (Group 1) and in 11 patients with ulcerative colitis (Group 2). The separation of white blood cells was achieved by a double density gradient technique The cells were incubated with radioactive butyrate and the radioactivity of carbon dioxide produced by butyrate oxidation was determined by scintillation counting. The detected radioactivity was translated into terms of biological activity as p mole per hour per million cells (pmol/h/m) of oxidized butyrate The results were: in Group 1 lymphocyte butyrate oxidation ranged from 5·6pmol/h/m to 223pmol/h/m and for granulocytes from 0pmol/h/m to 23·7pmol/h/m In Group 2 values ranged from 26pmol/h/m to 163pmol/h/m for lymphocytes and from 0pmol/h/m to 13·8pmol/h/m for granulocytes Our conclusions are that the rate of butyrate oxidation is greater in lymphocytes than in granulocytes in both disease and control groups ($P < 0·001$) There are no differences in this metabolism in lymphocytes and granulocytes between the disease and control groups ($P = 0·43$) These data imply that there is no genetic defect of butyrate oxidation in ulcerative colitis patients

Adult Hirschsprung's disease: a case report

R. Buzzacchi, G. Mariani, C. Bosi and M. Andreoli *Division of General Surgery, Ospedale di Ostiglia, Italy*

Concerning surgical strategy, several technical choices are available that can be applied in standard routine operations, after careful evaluation of the various anatomofunctional parameters.

In our case, a double colostomy (right and left) is reported to have been set up as an emergency in order to relieve the large bowel and to restore the functionality of the non-pathological tract, followed (6 months after the acute event) by surgical definitive therapy, consisting in total rectocolectomy and subsequent transit restoration by ileo-anal anastomosis with a J-pouch interposition.

Rectal cancer surgery: our experience

I. Caristo, E. Auxilia, W. Panichella, M. Bianchi, G. Buluggiu, G.P. Arzillo, U Cosce and P. Cavaliere *Divisione di Chirurgia Generale, Ospedale S. Paulo USL, 2 Savonese via Genova, 17100 Savona, Italy*

During the period 1989–1996, 170 patients underwent surgical invervention for rectal cancer at our Surgical Department. There were 91 men and 79 women in the group, with an average of 68 years. The cancer stages were in the following Dukes A 18 carcinomas, Dukes B 72 carcinomas, Dukes C 56 carcinomas, 24 locally advanced cancers (Dukes D). Localization of the tumours were: 38 in distal rectum, 58 in middle rectum, 74 in proximal rectum. One patient presented a double synchronous localization in rectum and left flexure of the colon. Forty-six interventions without anastomosis were performed· 12 explorative laparotomy, four Hartmann procedure and 30 abdominoperineal Miles resection.

In the 50 very-low rectal anastomosis and 45 in the other 68 performed in high lesions, an EEA disposable stapler was utilized through the anal canal, in such cases by the 'Knight-Griffen' technique. In six patients a colon-anal sphincter-saving anastomosis was performed by non-absorbable monofilament. In the remaining 23 patients a hand-sutured end-to-end anastomosis with a single-layer running of absorbable monofilament 3-0 double-armed was performed

The post-operative mortality rate was less than 2 per cent (three patients) The surgical complications were seven (4 per cent); two anastomotic leakages were treated by a reintervention and five fistulas by conservative therapy. We have not used hydrosoluble contrast enema in post-operative period to detect subclinical leakages..

The 5-year actuarial survival was performed by Kaplan–Meier method The actuarial survival for the total patient group after 12, 24, 36, 48 and 60 months was, respectively, 83 per cent, 72 per cent, 66 per cent, 64 per cent and 61 per cent The data analysis regarding the single stages showed no mortality after 5 years in stage A, 82 per cent survival after 5 years in stage B and 41 per cent survival in stage C Fifty per cent of patients in stage D died after only 6 months and one patient is still alive 24 months after surgical treatment

Lateral resection margin (LRM) in rectal adenocarcinoma: evaluation of 54 cases

N. Carvalho, M. Brito and J. Giria *Hospital Garcia de Orta; Department of Surgery & Histopathology, Pragal, 2800 Almada, Portugal*

Aim: Rectal cancer local recurrence is a major cause of morbidity and mortality. For some authors, the main mechanism of local recurrence is due to LRM invasion. We have evaluated the degree of lateral spread of the resected tumour and related it to short-term recurrence rate

Patients and methods: In 54 patients operated for rectal adenocarcinoma (31 sphincter-saving operations, 19 abdominoperineal resections), during a 3-year period (1992–1995), the lateral resection margins were evaluated by Quirke's method and were considered positive if the distance from the outermost part of the tumour to the resection margin was less than 1 mm.
Results: The pathologist's adherence to LRM evaluation was 100 per cent. The exact distance was determined in 77 per cent with a mean of 1·3 cm (range 0·1 to 3·5 cm). LRM was positive in three cases So far, the only case of local recurrence occurred in a patient with positive LRM (mean follow-up period was 16 months).
Conclusions: (a) LRM can be evaluated in all resected specimens of rectal cancer (b) LRM positivity can influence postoperative therapeutics. (c) Further studies are still necessary to define the importance of LRM

Familial colorectal cancer: screening programme

C. Castro, J. Giria and M.J. Brito *Hospital Garcia de Orta, Surgery and Histopathology Department, Pragal, 2800 Almada, Portugal*

Introduction: Colorectal cancer (CRC) is responsible for a large number of deaths every year, all over the world. The results of treatment of advanced disease are still poor, so early detection is the best option to improve outcome (primary and secondary prevention). This has contributed to greater interest in CRC aetiology, particularly as it relates to high-risk groups such as those with a hereditary predisposition to this disease. Approximately 25 per cent occurs in people who have a family history of the disease. Hereditary non-poliposis colorectal cancer (HNPCC) or Lynch Syndrome is a familial CRC with an autosomal dominant inheritance pattern and accounts for approximately 4–6 per cent of the total CRC burden The Amsterdam Criterias proposed by the International Collaboration Group in 1990 should be fulfilled for its identification
Description: We present our experience so far of screening individuals referred to our Hospital because of their positive familial history of CRC, particularly Lynch Syndrome, since 1994 with the results of the follow-up of patients and their relatives. The screening programme involves full colonscopy at 2–4-year intervals, on individuals over 25 years of age. Families were subdivided according to family history in two groups. (a) two families conformed to the Amsterdam Criteria for HNPCC: 15 asymptomatic first-degree relatives were offered surveillance; (b) 12 families did not conform to all of the Amsterdam Criteria. 76 asymptomatic at-risk members, were offered surveillance
Results: Three subjects (20 per cent) of the HNPCC families accepted screening. Twelve subjects (16 per cent) of suspected families accepted surveillance. After initial colonoscopy, abnormalities were found in two HNPCC subjects. We found dysplastic tubular adenoma in one relative and several hyperplastic polyps in another
Conclusions: The compliance rate of screening programme was low. High-risk group screening allows a better control and education of the population, and probably reduces death from CRC in individuals with a strong family history of CRC and provides an opportunity for primary and secondary prevention.

Generalized peritonitis in sigmoid acute diverticulitis: surgical treatment—a randomized study of French Research Associations

B. Celicout and G. Zeitoun *French Research Associations, bvd Haussmann, 75008 Paris, France*

Generalized peritonitis in sigmoid diverticulitis is a rare disease and surgical management of this complication is still controversial Common practice is immediate radical surgery (Hartmann operation) or conservative surgery (perforation suture if visible and colostomy, followed by a second time surgery with resection-anastomosis). The aim of this report was to compare those two surgical treatments in a multicentre randomized study.

Materials and methods: Generalized peritonitis was defined as presence of pus (purulent peritonitis) or faeces (stercoral peritonitis) in free abdominal cavity Acute sigmoidy was defined as an inflammatory fixed lesion with the perforation upon it. Randomization was done during the operation, stratified by age <65 years and ≥65 years. Antibiotherapy had to be associated with surgical treatment (metronidazole was mandatory) and a minimum of 6 litres physiological serum lavage of the peritoneal cavity (with or without antiseptic). Following reinterventions were resection and colo-rectal anastomosis, or continuity restoring after Hartmann operation (free surgical technique). The main judgement criterion was the first operation mortality. Secondary criteria were morbidity, number of operations, and total duration of hospitalization.
Results: From February 1992 to February 1996, 113 patients were included (13 were excluded a posteriori). Of the 100 patients analyzed, the mean age was 67 ± 15 years. Sex ratio was 1·1. Forty-five have had a conservative treatment (CT) and 55 a resection (R) (53 Hartmann and two immediate anastomosis) Global mortality was 22 per cent ($n = 22$): 22·2 per cent ($n = 10$) after CT and 21·8 per cent ($n = 12$) after R The early reintervention rate was higher after conservative treatment [20 per cent ($n = 9$) *vs* 5 per cent ($n = 3$), $P < 0·05$] (due to persistant peritonitis), and three operations were required in 14 [40 per cent ($n = 12$) *vs* 6·5 per cent ($n = 2$)]. Mortality was significantly increased by age ≥ 65 years [34·5 per cent ($n = 20$) *vs* 4·8 per cent ($n = 2$) $P < 0·01$], female sex [71·5 per cent ($n = 16$) *vs* 28·5 per cent ($n = 6$) $P < 0·05$], preoperative visceral complication associated ($P < 0·05$) There was no influence of presence of pus or faeces in the abdominal cavity. Concerning patient with a subsequent reintervention later, there was no difference between the two groups (resection or conservative) in terms of mortality, morbidity or hospital duration or complications
Conclusion: Mortality of generalized peritonitis in sigmoid acute diverticulitis was 22 per cent ($n = 22$) regardless of the type of initial surgical treatment (Hartmann resection or colostomy-drainage ± perforation suture). The significantly more important early reintervention rate and the greater frequency of three operations, leads to a preference for Hartmann type surgery for the treatment of generalized peritonitis in acute diverticulitis

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K-*ras* mutation in colorectal cancer: preliminary results of a prospective study

J.P. Cerottini*, S. Caplin*, E. Saraga†, J.C.I. Givel* and J. Benhattar† **Department of Surgery and †Institute of Pathology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland*

Aim: Initiation and progression of colorectal adenocarcinomas are related to mutations involving various oncogenes and tumour suppresser genes. Mutations involving the proto-oncogene K-*ras* have been described in colorectal cancer and may be related to tumour aggressiveness. The value of K-*ras* gene determination as prognostic marker is however not yet clearly established.
Patients and methods: The results from 99 consecutive patients recruited during the first two years of an ongoing prospective study analysing the effect of a K-*ras* mutation as a prognostic factor in colorectal cancer are reported
Results: Disease-free survival ($P = 0·02$) and overall survival ($P = 0·03$) were significantly worse for patients harbouring a K-*ras* mutation. Analysis of the mutation type determined a tendency towards a reduced disease-free interval for 12-TGT ($P = 0·04$) and 13-GAC substitutions ($P = 0·002$) only. Patients with one or other of these had a 2-year disease-free survival rate of 42 per cent compared to the 76 per cent of the group of patients harbouring either another mutation type or a wild type status ($P = 0·001$).
Conclusions: The results herein presented suggest that K-*ras* acts as a prognosis factor in colorectal cancer and that this effect is probably related to a limited number of defined mutations. K-*ras* determination may be useful for follow-up and adjuvant therapies strategies in colorectal cancer.

Omentoplasty for perineal healing after abdominoperineal rectal resection: a prospective study

A. Charlier, A. Fingerhut and J.M. Hay *French Associations for Surgical Research, Hôpital Saint-Camille F 94360 Bry-sur-Marne, Hôpital de Poissy F 78303, Poissy, Hôpital Louis Mourier F 92701 Colombes, France*

Aim: To compare perineal healing with or without omentoplasty after abdominoperineal rectal resection for carcinoma.
Methods and patients: A prospective multicentre study, based in 15 centres (three University, nine non University teaching hospitals and three private clinics) reviewed 186 consecutive patients (between January 1983 and August 1990)· 21 were withdrawn because of protocol violation, leaving 165 for analysis.
Interventions: Abdominoperineal resection for adenocarcinoma of the distal third of the rectum followed by omentoplasty (OP) (n = 64) to the pelvis or not (NOP) (n = 101). Main outcome measures: rate of healed perineums at 1 month, the time interval to complete healing.
Results: Seven patients (4 per cent) died, four in OP and three in NOP (one perineal abscess). The immediate postoperative complications and median duration of hospitalization were similar The median time to complete healing, the rate of healed perineums at 1 month and the number of persisting sinuses at 12 months were similar. The number of secondary openings necessary was significantly higher ($P < 0\cdot05$) in NOP (16 *vs* 3). Ten late deaths occurred in the OP and NOP, one and five with local recurrence, respectively More recurrences occurred in NOP (1 *vs* 8 per cent not significant)
Conclusions: Although this study was non-randomized, the results suggest that OP to the pelvic space promotes perineal healing after abdominoperineal rectal resection for carcinoma by significantly decreasing the rate of secondary opening.

Perioperative blood transfusion and leak of rectal anastomoses

M. Chiarugi, P. Buccianti, O. Goletti, J.C. Galatioto, L. Decanini, R. Balestri, M. DiSarli and E. Cavina *University of Pisa, Department of Surgery, S. Chiara Hospital, 67, via Roma 56126 Pisa, Italy*

Background/Aim: Perioperative blood transfusion (PBT) has shown to increase septic complications after surgery. The purpose of this study was to determine whether any relationship exists between PBT and leaks of colorectal anastomoses.
Subjects and Methods: Retrospective analysis of data from 108 patients who had either a single or a double stapled anastomosis after anterior resection for rectal cancer Of these, 40 (37 per cent) received one or more packed red cell (PRC) units (mean 2 9, median 2·5, IR 2·0) before (n = 5), and during or within 72h after surgery (n = 39) Four patients received blood both pre- and postoperatively There was no instance of haemorrhagic shock. The group of transfused (n = 40) and the group of non-transfused (n = 68) patients were compared for age, sex distribution, height of the tumour, type of stapled anastomosis, adoption of covering stoma, stage of cancer, mortality, and occurrence of clinical leak
Results: Overall rates for mortality and dehiscence were respectively 3 per cent (n = 3) and 13 per cent (n = 14). Two deaths were recorded among transfused and one among non-transfused patients (5 per cent and 1 per cent, P = n.s.). The two groups did not show any significant difference also for age, sex distribution, height of the tumour, stapling type, stage of cancer, implementation of protective colostomy By contrast, leak rate was 30 per cent (n = 12) in the transfused group and 3 per cent (n = 2) in non-transfused ($P < 0\cdot0001$).
Conclusion: Occurrence of leak was significantly higher in patients who were transfused by PRC. This suggests that PBT, already known as a cause of cancer recurrence, might also negatively affect the outcome of stapled rectal anastomosis Should this suggestion be confirmed, it is another reason to be careful with blood administration in rectal cancer patients

Does major postoperative infection increase the risk of carcinological recurrence after proctectomy for cancer?

P. Chiotasso and A. Liagre *Department of Digestive Surgery, Pavillon Dieulafoy, CHU Purpan, Toulouse, France*

We do not know if major postoperative infection may affect the prognosis of cancer, while the immune defences are modified The aim of this study was to compare the prognosis of patients operated on for rectal cancer with a major postoperative infection (infected group) to the remaining cases (control group)

All the charts of patients operated on for rectal cancer between July 1977 and April 1993 were retrospectively reviewed. There were 586 consecutive cases: 393 were males and 193 females. The mean age was 64·1 years One hundred and fifty-nine patients (27·2 per cent) had a preoperative pelvic irradiation.

Twenty patients had a major postoperative pelvic infection and classified in the 'infected group'. Ten patients (50 per cent) had preoperative pelvic irradiation There were seven Dukes A, three B, nine C and one with distant metastases The carcinological mortality was, respectively, one case (14 7 per cent) for Dukes A, two (66·6 per cent) for B, six (66·6 per cent) for C and one (100 per cent) for distant metastases The total mortality was 10 cases (50 per cent) In the remaining 'control group' of 566 patients, 152 had a preoperative irradiation (26·8 per cent) There were 159 Dukes A, 190 B, 126 C and 91 distant metastases The carcinological mortality was, respectively, 10 cases (6·2 per cent) for Dukes A, 61 (32 1 per cent) for B, 57 (45·2 per cent) for C and 78 (85·7 per cent) for distant metastases The total mortality was 206 cases (36·3 per cent) in this group

There is a significant difference between the total mortalities in the two groups (50 per cent *vs* 36·3 per cent), (χ^2, $P < 0\ 0001$) There is a particular increased mortality in the infected cumulated group of Dukes B, C tumours compared to the non-infected corresponding control group (66·6 per cent *vs* 37·3 per cent), (χ^2, $P < 0\cdot0001$) thus, in the infected group, the chances of dying from cancer are almost twice the control group. However, it is noteworthy to see that there is more Dukes C and more irradiated patients in the infected group than in the control group.

In conclusion, it seems that major postoperative infections may affect adversely the carcinological prognosis of a rectal cancer.

Prognostic factors in colorectal cancer local recurrences

C Coco, C. Mattana, S. Coghandolo, R. Coppola, L. Carbone and A. Picciocchi *General Surgery Department, Patologia Chirurgica, Catholic University, Policlinico 'A. Gemelli' L.go A. Gemelli 8, 00168 Rome, Italy*

Aim: The aim of this study was to evaluate, in a group of patients suffering from colo-rectal cancer, the influence on local recurrence (LR) of some clinical and anatomo-pathological variables
Methods: The study was limited to 833 patients who underwent potentially curative resection and have been followed for at least two years. All patients were evaluated every 6 months for the first 3 years and yearly thereafter by means of clinical, laboratory, endoscopic and radiological investigations LR was observed in 78/833 patients (9·4 per cent), 19 of these had evidence of distal failure simultaneously (2·2 per cent) The incidence of LR was 2 4 per cent (11/455) and 17·7 per cent (67/378) in the carcinoma of the colon and rectum, respectively Median time of LR was 16 ± 11 months, 75 per cent (59/78) presents within 23 months from operation. Chi-square test was used to relate incidence of LR to clinical and anatomo-pathological factors and then a multivariate logistic regression analysis was used to evaluate the most significant variables
Results: Univariate analysis reveals a significant relationship between LR incidence and age under 50 years ($P = 0\ 01$), presence of preoperative complication ($P = 0\cdot01$), stage ($P = 0\ 01$), site of primary tumour ($P = 0\cdot000$) and lymph-nodal involvement ($P = 0\cdot0002$). No statistically significant difference was found between LR incidence and depth of tumour wall infiltration, number of lymph-nodes involved, grading and

morphology of primary tumour. Multivariate logistic regression analysis confirmed these results except for preoperative complication ($P = 0{\cdot}9$).
Conclusions: Authors believe that selection of patients to undergo adjuvant therapies is improved by identification of patients with high-risk of local recurrence.

The effects of operative decompression procedures on bacteraemia in experimental colonic obstruction

F. Coşkun, O. Cengiz, M. Kavurmaci, B. Bozkurt and M. Koç *Numune Hospital, 2nd General Surgery Clinic, Ankara, Turkey*

Besides the function of ingestion, absorption and secretion of the gut, it prevents penetration of luminal bacteria and endotoxins to the blood stream. This function is performed by means of well differentiated immune system and local barrier properties of the intestine. A variety of causes including intestinal obstructions that could alter the function have been documented in clinical and experimental studies Intraoperative decompression of distended parts of an intestine after relief of obstruction used by many investigators. Decompression procedures have many advantages, but it was demonstrated that they promoted bacteraemia when used in small intestinal obstruction. The incidence of bacteremia after decompression procedures commonly used in colonic obstruction has been investigated. Twenty-four Winstar albino rats were used and the rats were randomly divided into three groups, each containing eight rats. The first was allocated as control group in which only laparotomy and blood cultures were performed. Colonic obstruction was created by ligation of the bowel at the rectosigmoid junction, in the second and third groups during the first operation Twenty-four hours later in the second laparotomy, the obstructions were released in both groups and antegrade stripping was tried in the third group only. Consequently blood cultures were obtained There was no statistical difference either between the controls and the others, nor between the second and third groups for incidence of bacteraemia.

Surgical management of obstructed carcinoma of the left colon and rectum

K. Daskalakis, E. Anagnostou, P. Vernikos and G. Diamantopoulos *3rd Surgical Department, Evangelismos Hospital, 45–47 Ipsilandou Str. 10676, Athens, Greece*

Aim: The surgical treatment of obstructive carcinoma of the left colon and rectum remains controversial. The aim of this study is to indicate the problems in management of such patients and the advantages of one-stage resection and immediate anastomosis.
Materials and methods: During the last 6 years (1900–1995), 156 patients with lesions on the left colon and rectum were operated on (94 electives, 62 emergencies) in the 3rd Surgical Department of the Evangelismos Hospital. Of 62 patients who required emergency operations, 37 (14 males, 23 females) had obstructed carcinoma of the left colon or rectum. The age of the patients ranged between 47 and 91 years. The procedures were: left colectomy and immediate anastomosis in 18 patients (48 6 per cent), subtotal colectomy and ileosigmoid anastomosis in 3 (8·1 per cent), Hartmann's procedure in 13 (35·1 per cent) and loop colostomy in three patients (8·1 per cent). One protective colostomy was made.
Results: Mean hospital stay was 12 days in patients with resection and anastomosis. Three anastomotic leakages were observed which were managed conservatively. There was no postoperative death from anastomotic leakage Other complications were observed in 10 patients (27 per cent) postoperatively
Conclusions: In the surgical management of obstructed carcinoma of the left colon and rectum, one-stage resection with immediate anastomosis, if possible, presents better results than the other procedures. Protective colostomy is not necessary.

Actinomycosis with its intestinal presentation and indication for operative treatment

G. Denkov, M. Ristov and S. Decovski *Medical Centre of Stip, Republic of Macedonia*

Aim: Example of the case of actinomycosis with its intestinal presentation, location (in the sigmoid), and indication for operative treatment uncommon in abdominal surgical cases.
Material and methods: In 1993 a female patient aged 52, a farmer by profession, was operated on for an acute form of appendicitis. In the next 2 years (1993–1995), during the regular examinations (clinical, ultrasound and X-ray), ileitis as well as light anaemia was confirmed. With all these methods we could not determine the illness which has caused this unusual condition, therefore we decided for explorative laparotomy.
Results: During the operation a 20-cm long tumour was found on the sigmoid colon. A partial resection was done and continuity of the sigmoid was end-to-end anastomosis.
Pathohistological result: *Actinomices bovis crasi* (Sigme) were found The patient was treated with Penicillin (parenteral and oral) in the next 4 months and with antimicotics (Nystatin, Amphotericin B at 250mg). At the control examinations every 6 months (1996) the results have been satisfactory
Conclusion: We think that this rare case of an intestinal form of Actinomycosis will remind people of the diagnosis of this illness and the treatment by sigmoid colon resection. Before this treatment a copro- and haemo-culture should be done, but the main significance is the histopathological and microbiological diagnostics of the resected material.

Predictors of survival after curative resection of carcinoma of the colon and rectum

H. Dogan, C. Dener, N.A. Kama, U. Gözalan and H. Yavuz *Ankara Numune Hospital, 4th Department of Surgery, Ankara, Turkey*

Introduction: Prognostic factors, derived from clinical, laboratory and pathological data of colorectal cancer patients are important for the determination of high-risk groups for recurrent disease and follow-up.
Patients and methods: Data on 38 patients who had curative resection for colorectal carcinomas between 1990 and 1995 were studied to determine the independent effect on recurrence and survival of several factors using log-rank test, Cox regression model and logistic regression analysis with SPSS for windows statistical program.

The age, sex, site of tumour, tumour size, serum CEA level, haemoglobin levels, chemotherapy, tumour fixation, tumour obstruction, tumour perforation, blood transfusion, Dukes stage, Kirklin stage, Astler–Coller stage, GITSG stage, TNM stage, Jass stage, Harrison stage, type of tumour, neuroendocrin component, signet ring cells component, tumour differentiation tubule configuration, cribriform pattern, papillary configuration, pleomorphism, loss of polarity, desmoplasia, necrosis, mitosis count, perineural invasion, vascular invasion, peritumoural lymphocytic infiltration, Crohn's-like lymphoid reaction, dentritic cells, mast cells, eosinophils, PMN leukocytes, metastatic tumour nodules in pericolic fat, metastatic nodes, lymph node reaction patterns were evaluated in recurrence and survival analyses.
Results: The parameters found significant for survival in univariate analysis were. perineural invasion, intramural vessel invasion, signet ring cells, metastatic nodes, tumour necrosis, sinus histiocytosis, site of tumour, tumour fixation, chemotherapy and Harrison stage. The parameters found significant in univariate analyses for recurrent disease were: serum CEA levels, intramural vascular invasion, desmoplasia, tumour differentiation, metastatic nodes, lymph node reaction score, necrosis and sinus histiocytosis.
Conclusion: Significant parameters in univariate analysis were included in Cox model for multivariate analysis. Tumour fixation, perineural invasion and sinus histiocytosis were independent parameters for survival. Using logistic regression analyses lymph node reaction pattern score, sinus histiocytosis and site of tumour were independent parameters for recurrent disease.

Morbidity and mortality for lymphadenectomy in surgery for rectal cancer

P. Esposito, D Cerbone, S. Perrotta, S Verde and G. Cerbone
Department of Surgery, University Federico II and Department of Emergency, New Pellegrini Hospital, Naples, Italy

Lymphadenectomy represents a fundamental phase in the surgical approach to rectal cancer to assess the staging of neoplasm. The goal of this study is to define the morbidity and mortality of a radical resection for adenocarcinoma of the rectum complemented by a wide pelvic lymphadenectomy.

A group of 15 patients (six males and nine females, mean age 64 years, range 45–76 years) with rectal carcinoma who underwent a surgical resection with wide pelvic lymphadenectomy was compared to a similar group (five males and 10 females, mean age 63 years, range 45–76 years) that underwent surgical resection with a conventional lymphadenectomy. There were no deaths. Mean intraoperative blood loss was similar in the two groups, although five patients (33 3 per cent) required blood transfusions during the performance of a wide pelvic lymphadenectomy in comparison with only three (20 per cent) during conventional pelvic lymphadenectomy. The rate of early postoperative complications and the average length of postoperative hospital stay were each similar between the two groups. After a wide pelvic lymphadenectomy, three (18 per cent) patients developed a neurogenic bladder, requiring intermittent self-catheterization, and they all except one recovered within 3 and 8 months, respectively Of the 11 males, three from the first group and three from the second group were sexually active before surgical treatment. After surgery, only one patient from first group regained his sexual potency whereas in the second group the recovery was total We conclude that the performance of a wide pelvic lymphadenectomy, despite the observed complications, in skilled hands, does not increase the intraoperative or early postoperative complication rate, the mean intraoperative blood loss, or the length of postoperative hospital stay.

Defective functional response in peripheral blood mononuclear cells from colorectal cancer patients

F. Esquivel*, F. Carrión*, T. Ratia‡, E. Reyes*, A. Prieto*, M P Hernandez* and M Alvarez-Mon*† **Department of Medicine, University of Alcalá de Henares, †Immune System Diseases Service, ‡General Surgery Service, Hospital Príncipe de Asturias, Universidad de Alcalá. Ctra. N-II, Km 33.600 Alcalá de Henares (28871), Madrid, Spain*

Aim: The association between the progression of colorectal cancer (CC) and alteration in the functions of immune system have been investigated The functional response (proliferative and cytotoxic) and the phenotypic profile of peripheral blood mononuclear cells (PBMCs) from CC patients were studied.

Materials and methods: The PBMCs from 39 patients with CC (15 patients belonged to stage B, 14 patients belonged to stage C and 10 patients corresponded to stage D of the Dukes system) and 21 healthy controls were obtained by Ficoll-Hypaque gradient centrifugation The proliferative response was measured by [^{3}H]-thymidine uptake during the last 18h of 4 days' culture, with phytohaemagglutinin (PHA) and phorbol esters (TPA) stimulation alone or in combination with interleukin-2 (IL-2) The cytotoxic activity was also measured by ^{51}Cr liberation assay. Target cells were K562 (NK-sensitive) or Jy (NK-resistant), effector cells were stimulated with various cytokines for 18h prior to the assay The phenotypic study was assessed by flow cytometry analysis

Results: The proliferative response of PBMCs from CC patients (Dukes stage B, C and D) to PHA was found to be significantly lower than that observed in those from healthy controls. The addition of exogenous IL-2 significantly restored this defective proliferative response in stage B and C but not in stage D In CC patients at stage B, the proliferative response to TPA was similar to that observed in healthy controls However, the CC patients in C and D stages showed a proliferative response significantly lower than that of the healthy controls The addition of exogenous IL-2 corrected this defective proliferative response There were no significant differences in the cytotoxic activity of PBMCs to K562 or to Jy target cells between CC patients at stage B and C of Dukes and healthy controls. However, the CC patients at stage D showed a cytotoxic response significantly lower than that of the healthy controls. This functional abnormality was corrected with the addition of IL-2 The addition of IL-4 or IL-6 could not correct this defective cytotoxic activity. The percentages of CD56+ and CD57+ positive cells were similar in PBMCs from CC patients in D stage and healthy controls. However, these percentages were significantly higher in B and C stage of the disease than that observed in healthy controls.

Conclusions: These findings suggest that the CC patients, at more advanced stages of the disease, seem to display an impaired immunological response that could explain the poorer clinical prognosis of these patients

Two-stage fistulotomy in complex anal fistulas: a retrospective review of surgical and functional results

G.P. Ferulano, S. Dilillo, S. La Manna, F. Scala and G. Coppola *Surgical Oncology, 3rd Division of Surgery, Faculty of Medicine, Federico II University, via S. Pansini, 5, 80131 Naples, Italy*

Complex anal fistulas according to Parks' classification account for 10–20 per cent of fistula series and are usually difficult to manage. We report our experience of the two-stage fistulotomy.

Material and methods: The record cards of 271 patients (mean age 48 years) who had undergone primary or recurrent surgery for fistula in-ano from 1980 to 1994 were reviewed The operative records identified 49 patients (18·1 per cent) with complex anal fistulas needing to be treated by a two-stage technique of wide laying open of the distal track and application of a nylon Seton around the external sphincter (ES) or the puborectalis, tightened until the ES was divided, or left in place loose until an adequate fibrosis allowed the sphincter cutting

Results: All patients were followed for 1 year or more to evaluate the results (endoscopy, manometry), 44 of them responded to a call for follow-up 3–4 years later Fistula persisted or recurred in four patients (8·1 per cent), minor continence disorders (soiling, urgency) occurred in 11 patients (22·5 per cent), none referred to faecal incontinence. Statistical analysis show that the site and the level of the internal opening, but not the way of cutting the ES, influenced the overall outcome.

Conclusions: Failures or continence impairment after two-stage surgery of complex anal fistulas have to be expected. The use of the Seton did not prevent some unsuccessful results but never caused severe complications in our experience

Management of acute pseudo-obstruction of the colon (Ogilvie syndrome)

C. Fotiadis, D. Mandrekas, A. Macheras, T. Liakakos, I. Karageorgos, A. Georgiou and M. Sechas *3rd and 2nd Surgical Departments, School of Medicine, Athens University, Athens, Greece*

The records of 22 patients with acute pseudo-obstruction of the colon over a 20-year period are reviewed. There were 10 men (45 per cent) and 12 women (55 per cent) with a mean age of 72·8 years Abdominal distension was present in all patients and in 12 cases palpation of the abdomen revealed diffuse tenderness. Abdominal radiographs, where feasible, demonstrated colonic dilatation in all cases. Eight patients were treated with intravenous fluids, nasogastric tube decompression and rectal tube. In three of the eight patients colonoscopic decompression was successfully performed. Fourteen patients required operative treatment; eight underwent tube caecostomy and six transverse colostomy.

In conclusion, acute pseudo-obstruction of the colon requires fast and proper treatment because of the danger of perforation and the high mortality rate.

Faecal continence is not adversely influenced by the level of coloanal anastomosis

R. Gamagami, G. Istvan, P. Cabarrot, A. Liagrea, P. Ghiotasso and F. Lazorthes *Hopitaux de Toulouse, Hopital Purpan, Place du Docteur, Baylac 31509, Toulouse Cedex, France*

Aim: To demonstrate if the level of coloanal anastomosis influences faecal continence following total proctectomy for low-lying carcinomas of the rectum.

Methods: From June 1977 to December 1993, 207 patients (145 males and 62 females, mean age 60 years) with middle and lower third rectal carcinomas underwent total proctectomy with coloanal anastomosis. Nineteen patients were excluded from the study, two suffered immediate postoperative deaths (mortality <1 per cent), 5 failed to have colostomy closures, nine had early deaths from metastatic disease, and three had completion proctectomies. Of those remaining, 155 patients (80 per cent) underwent synchronous abdominotrans-sphincteric resection, 27 patients (14 per cent) underwent resection with stapled coloanal anastomosis, and six patients (4 per cent) had transanal anastomosis

Prospectively, 188 patients were submitted a questionnaire at intervals of 3, 6, 12, 24, 36, 48 months to complete. Functional results were assessed in accordance with the Kirwin–Fazio classification. Patients were categorized according to the level of their coloanal anastomosis from the anal margin into three groups: (a) 42 patients with anastomosis at <2 cm, (b) 74 patients with anastomosis at 2–3 cm, and (c) 72 patients with anastomosis at 3 cm.

Results: One hundred and forty patients and 75 patients completed the questionnaire at 1 and 2 years, respectively. At 1 year after surgery perfect continence was present in 13 of 28 (46 per cent) of Group 1, 34 of 56 (60 per cent) of Group 2, and 29 of 56 (51 per cent) of Group 3. Similarly, at 2 years seven of 14 (50 per cent) of Group 1, 28 of 35 (80 per cent) of Group 2, and 20 of 26 (76 per cent) of Group 3 had maintained excellent faecal continence No statistically significant difference could be established between the three groups ($P > 0{\cdot}5$) both in the 1- and 2-year follow-up.

Conclusion: This study illustrates that the distance from the anal margin to the coloanal anastomosis subsequent to total proctectomy for carcinoma of the middle and the lower third of the rectum does not influence faecal continence in a statistically significant fashion. Furthermore, extrapolation of these findings can lead to the conclusion that the division of the superior portion of the internal sphincter does not influence the functional quality of continence in a significant way

Flow cytometric study of DNA index and S phase in colorectal cancer

J. Gómez, C. Piñol, J. Tarragona, J.M. Reñé, J. Buenestado, J. Ramos, J. Macià and J. Viñas *Faculty of Medicine, University of Lleida, Arnau de Vilanova University Hospital, Lleida, Spain*

DNA aneuploidy and S-phase have been associated with histopathological parameters, prognostic variables and outcome in colorectal cancer.

Flow cytometric DNA histograms of 124 paraffin-embedded samples of patients with colorectal cancers were evaluated for the association of tumour site, Dukes stage, lymph nodes with metastatic deposits, with patient survival

Patients operated on for Dukes B or C colorectal cancers at the Arnau de Vilanova University Hospital between 1986 and 1989 were included in the study. Study was closed in March 1996. Demographic, clinical and histopathological variables at the diagnostic were recorded. The samples of colorectal cancer of the same blocks used for the diagnostic were prepared using a modification of the method described by Hedley 1×10^6 nuclei were stained with a solution of ribonuclease and propidium iodide. Flow cytometry was performed on a EPICS PROFILE II instrument. The DNA histograms of 20,000 events were analysed using the Multicycle software.

DNA aneuploidy was found in 78 patients and mean S-phase was 17·24 ± 12·3 per cent. No association was found between age, sex, DNA results, clinical and histological pattern of colorectal cancer with survival A poorer prognostic was found in patients with lymph node metastatic affectation ($P = 0{\cdot}02$). DNA aneuploid tumours showed higher S-phase values ($P < 0{\cdot}001$)

New trends in diagnostics and treatment of colorectal cancer

N. Jaramov, I. Vijachki, D. Vijachki and C. Petkov *Medical University of Sofia, University Hospital 'Queen Joanna', 8, Bjalo more Street, Clinic of Emergency Surgery, Sofia, Bulgaria*

Colorectal cancer is one of the most common cancer diseases of the gastrointestinal tract in our country. For 1994 the morbidity rate rose to 26·6 per 100,000 individuals and the mortality rate to 19·5. During the study period of 1985 to 1995, 1000 patients with colorectal cancer underwent operation In 673 patients we found complications of the main disease· obstructive ileus, tumour perforation and diastatic bleeding from the rectum, paratumour abscess, local regional form with distant metastases. The following tests were performed on 50 patients: microbiological assessment of large bowel flora, evaluation of total biliary acids content in faeces, using thin layer chromatography, cholesterol and serum β-lipoproteins, and corticosteroids Increase of biliary acids concentration in the faeces, significant dysbacteriosis, and decrease of serum cholesterol were found. Treatment of colorectal cancer is predominantly operative The following radical operations were carried out. right hemicolectomy, left hemicolectomy, subtotal and total colectomy, resection of the sigmoid colon, the Hartmann operation, low resections of the rectum, extirpation of the rectum The new trends in operative management consist of lymphadenectomy and compulsory ligation of the inferior artery and vein, and left hemicolectomy for cancer in the left colon, right hemicolectomy for cancer in the right colon, subtotal colectomy with lymphadenectomy for the transverse colon A screening programme with haemo-occult tests was performed. The new principles of surgical treatment of colorectal cancer have resulted in a significant increase in the 5-year survival rate which is 57 per cent for T_4.

The value of faecal occult blood test in the postoperative follow-up of patients with colorectal cancer

I.G. Karaitianos, K. Tsamakidis, A. Karaitianou-Velonaki, D. Xynopoulos, G. Plataniotis, J.A. Karagiannis and E. Paraskevas *Surgical Oncology and Gastroenterology Departments, Hellenic Anticancer Hospital 'St. Savvas', Athens, Greece*

Early detection of local recurrence after radical resection for colorectal cancer is of great importance because early diagnosis of recurrence can prolong life expectancy in those patients who are candidates for reoperation A considerable drawback in the above strategy of follow-up is the increased cost of endoscopic, imaging, biochemical and scintigraphic tests as well as tumour markers levels, which renders their systematic application very costly or even impossible. The aim of the study was to assess and correlate faecal occult blood test in patients having radical resection for colorectal cancer with double contrast barium enema and colonoscopy in the detection of local tumour recurrence.

Sixty patients entered the study so far with a minimum follow-up period of 24 months The study protocol consisted of faecal occult blood tests (Hemodetect, Adelco), three samples each time, every 3 months for the first 2 postoperative years followed at 6-month intervals for the next 3 years.

Forty-one of the 60 patients had three or more negative tests. Double contrast barium enema or colonoscopy was negative in 37 and positive in four (two with colonic polyps, two with diverticular disease) but none with tumour recurrence. In the remaining 19 patients faecal occult blood test was positive in one or more samples and double contrast barium enema or colonoscopy showed tumour recurrence in five, benign polyps in seven, angiodysplasia in one and haemorrhoids in four. Two patients were repeatedly negative in both examinations.

Even if the number of patients studied is relatively small, it seems that a faecal occult blood test, despite a small percentage of false-positive or negative results, is an effective, easy and low-cost test for early detection of intraluminal tumour recurrence in the follow-up of patients operated on for colorectal cancer, but further prospective studies are needed

The impact of recurrent disease after surgical intervention for colorectal carcinoma on survival time

F.E. Klee[*], B.R. Osswald[†] and S. Wysocki[*] *[*]Departments of Surgery, Salem Medical Center, Zeppelinstr. 11-33, D-69121 Heidelberg, [†]University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany*

The impact of different types of recurrent disease after surgery for colorectal carcinoma may play a role in the decision as to whether a more aggressive or conservative treatment will be performed to prolong survival at the best possible quality of life.

We performed a common close date follow-up by questionnaire in 669 patients who underwent surgical treatment for colorectal cancer from 1985 to 1992. The maximum observed follow-up time was 104 months, the lowest right censored survival time was 12 months. Statistical analysis was performed using the Wilcoxon χ^2 test and Student's t-test.

In 124 patients, recurrent disease occurred The distribution of age and sex showed no significant difference to patients without recurrent disease. The distribution pattern of recurrent disease was as follows: recurrent disease isolated localized at the anastomosis occurred in 37 patients, isolated positive lymph nodes in 10 patients, solid or multiple liver metastasis in 34 patients, a recurrence in at least two localizations in nine patients, recurrent disease of further localizations in 30 patients, and a second carcinoma in four patients Although the localizations of recurrent disease were different, the survival times related to the time of surgical treatment for the primary tumour showed a very tight distribution, expressed by the Wilcoxon χ^2 test with 5 degrees of freedom of a P close to 1 ($P = 0{\cdot}9169$). A highly significant difference occurred between patients with and without development of recurrent disease, respectively (Student's t-test, $P < 0{\cdot}001$).

In conclusion, different patterns of recurrent disease in patients with colorectal carcinoma seem not to influence significantly the overall survival. Once a recurrence is diagnosed, the expected survival time is significantly lower compared to patients with no recurrent disease These results prove the necessity of a careful decision, whether an aggressive or a more conservative treatment will be justified to maintain the best possible quality of life

Pelvic ileal reservoirs

G. Kobakov and Temelkov *Medical University Varna, 9002 Marin Drinov str. 55 Varna, Bulgaria*

Since 1983 till May 1996 pelvic ileal reservoirs after proctocolectomy were constructed in 25 patients (14 males and 12 females). Twenty-two of the patients suffering ulcerative colitis and three familial adenomatous polyposis All of the cases were diagnosed by the means of preoperative colonoscopy and histological examinations In 18 cases an S-pouch was constructed while in five a J-pouch was made In 22 of the cases a one-stage operation was performed while in three a protective ileostomy was done. A long-term follow-up, regarding number of defecations, continence and potency was done in 20 patients. The early and late postoperative complications are discussed A modification of performing the ileoanal anastomosis after demucosation of the anal canal is presented.

The place of systemic lymphadenectomy during the radical resection of rectal cancer

M. Kontić *Surgical Clinic KBC Zvezdara, D. Tucovića 161, 11000 Belgrade, Yugoslavia*

Systemic lymphadenectomy plus high ligature of an inferior mesenteric artery provides the opportunity of cleaning all pelvic floors These are the most frequent places of recurrences of rectal cancer

The three most important parameters as a result of the treatment of rectal cancer (five years survival rate, percentage of recurrences and a number of specific complications) are analysed in two groups of patients From 1986 to 1990 312 curative operations for rectal cancer were performed The prospective group treated with lymphadenectomy and pelvic cleaning of 98 patients (31·5 per cent) and the other group of 204 patients (68 54 per cent) were treated by the classic technique of abdominoperoneal amputation or anterior rectal resection.

The 5-year survival rate in the prospective group is 62 per cent (60 patients) and in the control group 40 per cent (82 patients), local recurrences were very low: 20 patients (18 per cent), with the prospective group and very high with the control group 123 patients (60 per cent). Specific complications (urinary, sexual and surgical) are fewer with control group seven patients (8 per cent), and higher with the prospective group 26 patients (13 per cent). There are no evident differences in the mortality rate with both groups at four patients (4 per cent) and 15 patients (7 per cent), respectively

We can conclude that in the treatment of rectal cancer one of the most important factors is the high ligation of inferior mesenteric artery and lymphadenectomy of all epi-, paracolic, principal and aortic lymph nodes as well as the pararectal fat tissue

Safe alternative to conventional anastomosis techniques: initial experience with the biofragmentable anastomosis ring Valtrac®

T. Kovács, I. Koves, Z. Sulyok and I. Besznyák *Department of Surgery, National Institute of Oncology, Budapest, Hungary*

Initial experience and early results in clinical application of the biofragmentable anastomosis ring (BAR-Valtrac®) in digestive surgery is presented

From November 1993 to March 1996 the Valtrac ring was used in 36 cases, and one gastrojejunal, four jejuno-ileal, five small bowel-colon and 26 intraperitoneal colonic anastomoses were performed. All patients were operated on for malignant tumours (radical or palliative operations), and received conventional (mechanical, dietary and antibiotic) bowel preparation. Intraoperative technical difficulties occurred in six patients (purse string failure, serosal split), in two cases the BAR placement was abandoned. Postoperative complications related to the BAR appeared in three patients: clinically relevant anastomotic leakage occurred in two cases (5·5 per cent), and one case of mechanical ileus also occurred This was produced by distortion of the inserted ring They observed no other postoperative complications related to the compression anastomosis technique. Mean postoperative hospital stay was 8 days.

Based on this initial experience the most frequent causes of intra- and postoperative complications are analysed and the ways in which they can be avoided. According to this initial experience and the literature data, using the new anastomotic device a safe, atraumatic and sutureless bowel anastomosis can be performed The method is easy to learn and a standardized technique is used at different bowel segments in various conditions.

Bile, peripheral and portal blood CEA levels in detection of occult hepatic metastases in colorectal cancers

S. Kutun, C. Koksoy, B. Çetin, S. Kara, O Tarcan and A. Çetin *Department of Surgery, Ankara Oncology Hospital, Ankara, Turkey*

The aim of this study was to find out the importance of bile, portal and peripheral blood carcinoembryonic antigen (CEA) levels in detection of occult hepatic metastases caused from colorectal cancer. .

The study consisted of three groups: the patients with colorectal cancer with hepatic metastases ($n = 20$), without hepatic metastases ($n = 20$) and patients with undergoing laparotomy for benign reasons ($n = 20$) In all patients intraoperative peripheral, portal blood and bile samples were collected for CEA level measurement by radioimmuno-assay

The CEA levels in all samples of the patients with hepatic metastases were higher than the ones of the patients without hepatic metastases ($P < 0{\cdot}001$). Furthermore bile and portal blood CEA levels were higher than the peripheral blood ($P < 0{\cdot}05$). During the follow-up period hepatic metastases were detected in patients who had high bile CEA levels ($P < 0{\cdot}05$).

The metastatic status of colorectal cancer is very important for assumption of prognosis and design of effective therapy. Bile and portal blood sample collection for CEA measurement may be useful for the detection of occult hepatic metastases and decision of adjuvant therapy measures.

Low anterior resection with colonic reservoir but without defunctioning stoma

M. Machado, S. Fürstenberg, S. Goldman and
C. Lenander *Ersta Hospital, Box 4622, 116 91 Stockholm, Sweden*

Colonic reservoirs as an alternative to straight anastomosis in low anterior resections were described in 1986 Several studies have shown an improved functional result using this procedure and also a relatively low proportion of anastomotic leaks. For safety, a defunctioning stoma has generally been used We have now performed a large series of reservoirs without the routine use of a defunctioning stoma.

Methods: Between October 1994 and March 1996 we have operated on 53 patients with rectal tumours using a colonic J-reservoir. Low anterior resection with total mesorectal excision was performed in all cases. The left colonic flexure was mobilized and the reservoir constructed using the descending colon or the proximal sigmoid. The size of the reservoir has been 7–8cm The anastomosis was constructed with a double or triple stapling technique (TA-30, CEEA 31, Auto Suture).

Results: The median anastomotic level from the anal verge was 4cm (2–5cm). Only three patients (6 per cent) had a defunctioning stoma peroperatively due to technical difficulties. Another three patients (6 per cent) developed an anastomotic leak postoperatively and were reoperated with a defunctioning stoma One of these patients died two months later of septic complications. The five other patients had an uneventful recovery but two of them have a permanent stoma.

Conclusion: The colonic reservoir is a safe alternative to straight anastomosis in low anterior resection The proportion of anastomotic leaks is low also in patients without a covering stoma.

Dmin chromosomes as prognostic marker in colorectal cancer

C.L. Maillo, M.A. Fernández-Peralta, E. Escalante,
P. Artuñedo, J.J. González-Aguilera and M. Moreno Azcoita
Servicio Cirugía General, Hospital Universitario Getafe, Ctra Toledo Madrid, Departamento de Genética, Facultad de Biología, UAM, Madrid, Spain

Cytogenetical analysis in sporadic colorectal adenocarcinoma (SCRC) is determining some chromosomal alterations in these tumours. One of these alterations in the presence of Dmin chromosomes (chr.) in tumour cells. Dmin chromosomes are small chromosomes formed by the overexpression of oncogenes.

Patients and methods: We have studied cytogenetically 31 SCRC. The samples were obtained from fresh tissues (normal mucosa and tumour) and peripheral blood cultures were used as controls The samples were processed immediately or/and cultivated following a short-term protocol, and the analysis was performed at 48h. We determined the presence of Dmin chr. in tumour cells and the findings were related to sex, age, location of the tumour, level of differentiation, Dukes stage and follow-up

Results: The presence of Dmin chr. is not related to sex, age or location of the tumours. Table 1 represents the characteristics of the tumours in correlation with the presence of Dmin chr

			Dukes Stage				Level of differentiation		Follow-up	
	No	Age	A	B	C	D	Well	Moder	Death	Months
Total	31	66·17	3	11	11	6	16	15	12	23·1
Dmin	14	65·66	0	3	5	6	6	8	11	16·61
No Dm	17	66·52	3	8	6	0	10	7	1	28·86

Conclusions: Of the tumours 45·16 per cent had Dmin chr. when they were analysed. This characteristic is related to the Dukes stage. When it is present it indicates a worse prognosis and a higher index of mortality in intermediate and advanced stages (B, C, and D). Dmin chr could be a marker of evolution of SCRC.

Age is not a risk factor in colorectal surgery

A. Marmorale, A. Gavelli and C. Huguet *Department of Surgery, Princess Grace Hospital, 98000 Monaco*

More and more frequently, colorectal resection is performed in elderly patients. Operative risk is controversial.

We prospectively studied 686 colorectal resections with handsewn anastomosis, 441 on patients <75 years old (mean 72·2 ± 9·5 years) (64·3 per cent), 245 patients ≥75 years old (mean 81·3 ± 4·7 years) (35·7 per cent). Group 1 (<75 years) included 72·3 per cent elective resection, 7·5 per cent urgent (during the first 24h) and 20·2 per cent semi urgent procedures. Group 2 (≥75 years old) was similar (64·9 per cent, 10·2 per cent and 24·9 per cent respectively). The rate of diverting colostomy was 11·6 per cent in Group 1 and 9·7 per cent in Group 2. Hospital mortality was 1·6 per cent (seven cases) in Group 1 *vs* 3·7 per cent (nine cases) in Group 2 (n.s.). After emergency procedures it was 12·1 per cent in Group 1 and 12 per cent in Group 2. Elective resection was responsible for 0·2 per cent mortality in Group 1 and 1·9 per cent in Group 2. Morbidity was 7 per cent in Group 1 *vs* 11·4 per cent in Group 2. In Group 2, one simple case of clinical anastomotic dehiscence was observed after elective resection (0·6 per cent) *vs* nine cases (2 per cent) in Group 1 (n s), eight of them being elective cases

Old age, in our global experience and non-selected study, does not appear as a risk factor and should not contraindicate colorectal surgery.

Tumours arising from muscularis mucosae of the rectum and sigma

J. Martín, M. Carbajo, M. García, F. Martín, D. Padilla,
R. Pardo, J.M. Ramia, A. López and J. Hernandez Calvo
General Hospital, Ciudad Real, Spain

Tumours arising from the muscular layer of the bowel are uncommon and extremely rare when localized in the colon and rectum Most of them arise from the external muscular layer or muscularis propria. Tumours originating in muscularis mucosae or in the vascular system are uncommon. Two hundred rectal leiomyomas and leiomyosarcomas have been described. Both tumours produce similar symptoms: rectal mass, bleeding, defecatory derangement and pain. Proctosigmoidoscopy is the best diagnostic procedure. Even if the pathologist can make differential diagnosis between leiomyoma and leiomyosarcoma by the number of mitosis, biological behaviour can be very variable. Tumours originated in the muscularis mucosae are polypoid, pedunculated, benign and most of them will be treated by a polypectomy without recurrence. Leiomyomas arising from the muscularis externa have a 60 per cent chance of recurrence after local treatment Sometimes the recurrence is as a metastatic leiomyosarcoma.

In high- or low-grade leiomyosarcoma and leiomyomas arising from the external muscular layer (more than 5 cm), radical treatment with free margins and resection of involved adjacent organs is the best treatment Radical approach will provide best control of the disease and higher survival rates. Radiotherapy and chemotherapy have not been of any benefit in these tumours. While biological behaviour of tumours from the muscularis mucosae is more benign than the ones arising from muscularis externa, these will always require long-term follow-up. Three tumours arising from muscularis mucosae of the rectum and sigma are presented

Results of the perianal inflammation (PAI) treatment

R. Maskelis *First Surgery Department, Marijampole Central Hospital, Lithuania*

PAI diseases — paraproctitis (PP) and anorectal fistula (FAR) — form more than 40 per cent of all rectal cases During 1986–1990, 46 patients were operated on, and during the last 5 years twice as many patients were operated on

Emergency cases of PP, where only incision is performed, show unsatisfactory results of higher recurrence levels, and longer duration of treatment. As of 1991 the Gabriel technique has been used in acute PP and FAR cases involving intrasphincteric (IS) or trans-sphincteric (TS) abscesses. The aim of this method is to abolish all channels connecting external (EO) and internal orifices (IO).

A modified Gabriel operation is used, whereby a finger or surface hook is used to find the IO, then an incision is made on the abscess 3–4 cm, through the anus in PP cases The abscess cavity is drained and cleaned All tissues connecting the EO and IO from the abscess cavity to the rectum are then opened. In extrasphincteric cases it is not usually possible to excise the IO, so in these cases a synthetic suture is passed through the IO, with which the incised tissues and anal sphincter are tied for the next 3–7 days If the IO is elevated, this must be performed twice (with a 1–2-day interval). In chronic inflammation cases (e.g. FAR), the channel is marked by colour contrast with methylene blue at the initial stage of the operation

Between 1991 and 1995, 94 patients were treated, with an age range of 23 to 70 years. The modified Gabriel operation was used in 37 patients (39 per cent) The localization of the seat of inflammation, using Goodsall's rule on Stelzner's classification was: anterior wall in nine cases (26 per cent), lateral in two (6 per cent), and dorsal wall in 23 (67 per cent). The duration of treatment in 1991 was 22 days, during which time only two per cent were operated on using the modified Gabriel operation. During the last 3 years, this operation has been used on half of the patients. The duration of treatment has decreased by a factor of two during the last 5 years, and there are no recurrent cases.

Is drainage after colonic resection-anastomosis useful? A multicentre controlled trial on 800 patients

M. Mathonnet, F. Merad, J.C. Paquet and H. Hennet *French Associations for Surgical Research, Hôpital Louis Mourier 95701 Colombes Cédex, France*

Prophylactic drainage after colonic surgery, though frequent, has never been proved to be useful A few controlled trials have been performed their results do not show any advantage with drainage However, because these studies were done on a small number of patients they are not convincing, which is why a multicentric controlled trial on an adequate number of patients has been performed.

Patients and methods: Over 4·5 years, 14 centres have studied 813 patients with an average age of 66 (13–5) years. there were more women (423) than men (390) All kinds of lesions were included Not included were patients who had not been resected without anastomosis, septic operations, emergencies or those with inadequate haemostasis No preoperative risk factor (obesity, thinness, cirrhosis, steroid, radio-chemotherapy or visceral insufficiency) excluded a patient from the trial The operative procedure was completed either with or without drainage This drainage used was sump drainage in the pelvis, in the abdomen it could be dependent (tube or corrugated) drainage The randomization was made at the end of the operation in four groups. intra-abdominal anastomosis (ileo or coelo-colonic) intrapelvic anastomosis (higher rectum, lower rectum or anus). The main criterion of judgement was anastomotic leakage clinically or radiologically, the secondary criteria were parietal complications, and abdominal complications (local or general peritonitis) The seriousness of leakages was judged by the reinterventions and death (in the whole group and in patients with an anastomotic leakage) The same analysis has been made on anastomosis in the pelvis and in the abdomen.

Results: Four hundred and one patients were randomized without drainage and 412 with drainage Seventeen were later withdrawn, all in the group without drainage, because the surgeon subsequently decided to put a drain in: 384 patients were not drained, 412 were drained The two groups were comparable regarding dermography, pre- and peroperative risk factors, illness operated on, kind of resection, location of anastomosis, and in the rate of protected anastomosis. In the group without drainage there were 15 anastomotic leakages (4–6 per cent) 12 peritonitis (localized or general), deep haematomas, 20 reinterventions and 13 deaths (three with a leakage) There was no statistically significant difference between groups. In the analysis, taking into account the location of the anastomosis (abdomen or pelvis), there were no statistically significant difference between the two groups with or without drainage

Conclusions: Prophylactic drainage after colonic resection-anastomosis does not reduce the rate or the seriousness of intra-abdominal complications whatever the location of the anastomosis; abdomen or pelvis. Prophylactic drainage, therefore, is useless.

Surgical treatment of colonoptosis

A.A. Musalev, A.V. Sherbinin and V.N. Grona *Donetsk State Medical University, Illicha avenue 16, Donetsk, 340003, Ukraine*

Colonoptosis occurs rarely and is a little studied anomaly of development of the large intestine and its ligamentous apparatus. The aim of the study was to determine symptoms and methods of surgical treatment of this pathology in children.

One hundred and sixty-nine children aged 4 to 15 years with colonoptosis were diagnosed and treated. The main clinical signs were abdominal pains and constipation. Studying the anamnesis data and disease symptoms allowed the identification of three stages: I — a compensation stage, II — a subcompensation stage, III — a decompensation stage. All the children with compensation stages underwent complex conservative therapy aimed at normalization of the moto-evacuatory function of the large intestine. In 23 children with the disease at a decompensation stage the conservative therapy produced no effect. That made us resort to operative treatment according to the usual technique.

The symptoms of surgical intervention were progression of impairment of the large intestine moto-evacuatory function, painful abdominal syndrome, presence of endogenic intoxication, failure of complex conservative therapy for 6–12 months. The surgical treatment included fixation of the colon at a normal anatomical level. To improve functional results and to prevent the disease recurrence the elongated middle part of the transverse colon was resected before fixation, the gastro-colic ligament was mobilized. Under the ligament the intestine was placed with anastomosis and fixed by suturing the free margin of the ligament under the displaced intestine to the posterior layer of the peritoneum.

Follow-up period was 1·5 to 14 years. All children are healthy. The results obtained allow the utilization of proposed means of operative treatment in colonoptosis when conservative therapy is not successful

Trauma of the anus and the rectum: report of 20 cases

J.-C. Le Néel, E. Letessier, M. Capelli, O. Armstrong and F. Genier *Clinique Chirurgicale A, CHU Hôtel-Dieu, 44035 Nantes Cedex 01, France*

Aim: The aim of the retrospective study was to evaluate the results of surgical treatment in case of trauma of the anus and the rectum.

Methods: During a 12-year period we treated 20 cases of injury of the anus and rectum There were two children (aged 2 and 10 years) and 18 adults.

In adult patients (14 males and four females) mean patient age was 35 years old (range 16–72 years). There were nine blunt (traffic road trauma), six sexual assaults, one gunshot, and four impaling injuries. Risk factors were present in four cases. Initial diagnosis was made in 16 cases We noted four cases of delayed diagnosis (range day 1–day 12). Shock was present in 10 cases. Other injuries were noted in seven cases. Initial examination and diagnosis work-up showed isolated rectal or anal injury in 13 cases and complex injuries in seven cases. Associated organ injuries were fractures (seven cases of pelvic fracture), urinary ($n = 3$) and vascular injuries ($n = 2$).

Results: Isolated injuries with initial treatment led to good results in 77 per cent. However, we observed two complete and one partial faecal incontinence. Mean patient stay was 16·7 days. Associated organ injuries needed multidisciplinary management: Treatment-associated bone fracture repair ($n = 6$), diverting colostomy ($n = 6$), vasculary and urinary repair ($n = 2$). One patient died peroperatively. Intensive care unit was mandatory in 16 cases and patients developed complications. Mean total period of stay was 70 days. Rectal ($n = 4$), sexual and urinary complications were observed in young patients

Conclusions: Our experience as well as literature review favour initial sphincter repair associated to diverting colostomy.

Results of surgery for colorectal carcinoma in elderly patients

A. Papachristodoulou, E. Misiakos, E. Evangelidakis, V. Karydakis, G. Kouraklis, C. Markopoulos and J. Gogas *2nd Department of Propedeutic Surgery, Athens University Medical School, Laiko Hospital, Athens, Greece*

The aim of this study is to examine any differences in clinical presentation, surgical management, pathological stage and postoperative outcome in patients with colorectal cancer aged over 75 years. The records of 478 patients operated on for colorectal cancer, in our Department, from 1983 through 1993, were retrospectively reviewed. The ratio male to female was similar in both groups. There were 146 patients (30·54 per cent) aged over 75 years (Group 1) and 332 patients (69·45 per cent) under 75 (Group 2). A slightly higher, but not statistically significant, number of left-sided lesions were found in the elderly group Elderly patients were admitted urgently in higher percentages than the younger group. A predominance in defunctioning colostomies and Hartmann's procedures was noticed in Group 1 comparing tó Group 2 ($P < 0{\cdot}05$ and $P < 0{\cdot}01$, respectively) There was a 43·2 per cent of lesions urgently treated in Group 1 classified as Dukes B, whereas the percentage in the same subgroup in younger patients was 24·4 per cent (n.s.). In Group 1, septic complications more frequently followed both elective and emergency operations Total morbidity was 19·18 per cent for Group 1 and 14·45 per cent for Group 2 (n s.), whereas mortality was 13 7 per cent for Group 1 and 2·4 per cent for Group 2 ($P < 0{\cdot}001$). Advances in gastrointestinal surgery and postoperative care have contributed to a reduction in perioperative morbidity and mortality in the elderly. However, age still remains a major risk factor for the outcome after surgery for colorectal cancer.

Sepsis influence in colorectal surgery

V. Paunescu and T. Spircu *University of Medicine and Pharmacy 'Carol Davila', Surgical Clinic 'Bagdasar', Sos. Berceni Nr. 10–12, Bucharest, Romania*

The purpose of the study is the analysis of correlations between mortality and several factors of sepsis type in colorectal surgery

The study of 638 cases operated in between 1986 and 1995 (456 with neoplasia) reveals sepsis in 110 cases. The aerobic and anaerobic germs invaded all the peritoneal cavity (41 cases) or just a part (20 cases) and determined the depression of host defence. The sepsis was established preoperatively (19 cases), intraoperatively (42) and/or postoperatively (49). The patient's age was predominantly over 60 (72 cases) The surgical procedure was radical in 78 cases of which 55 had imposed reintervention The classical statistical methods of analysis of mortality in association with these criteria reveals a strong correlation ($P < 0{\cdot}001$) with extension of pus (generalized *vs* localized peritonitis), the type of surgical procedure (radical *vs* palliative) and the presence *vs* absence of sepsis in the moment of the first surgical intervention. Weaker correlations were observed between mortality and sex ($P < 0{\cdot}01$, greater in women), respectively between mortality and existence of neoplasia ($P < 0\ 025$). There was no significant correlation between mortality and age of patient Methods and algorithms of multivariate statistical analysis, especially from the principal component analysis domain, were used.

The negative influence of sepsis in colorectal surgery is emphasized, especially if pus is present preoperatively, regardless of whether the main disease is neoplastic.

Clinical and pathological variables in prognostic evaluation of patients with colorectal cancer

N. Pietra, L. Sarli, B. Thenasseril, O. Choua, R. Costi and A. Peracchia *General Surgery, University of Parma, Ospedale Maggiore, via Gramsci 14, 43100 Parma, Italy*

Aim: To use statistical analysis to evaluate the effects of clinical and pathological variables on prognosis after curative resection of large bowel cancer and to assess the independent influence of each when all other factors were held constant

Materials and methods: The influence of patient sex, age, tumour site, presence of preoperative complications (obstruction or perforation), disease stage, extent of direct spread of the tumour through the bowel wall, lymph node involvement, histological type, tumour grade, labelling index and DNA index were examined as prognostic factors for overall survival and death from cancer in 721 consecutive patients with colorectal carcinoma operated on for cure from 1976 to 1993 Univariate statistical analysis was performed on each variable. For the investigation of the effects of different variable on survival, a logistic regression model was used.

Results: In this study, overall survival was associated with male sex ($P < 0{\cdot}002$), patient age ($P < 0{\cdot}02$), preoperative complications ($P < 0{\cdot}0001$), disease stage ($P < 0{\cdot}0001$), direct spread of the tumour ($P < 0{\cdot}0001$), lymph node involvement ($P < 0{\cdot}0001$), histological type ($P < 0{\cdot}01$) and grade ($P < 0{\cdot}01$). In the multivariate analysis overall survival was independently associated with disease stage ($P < 0{\cdot}0001$). Death due to colon cancer was associated with disease stage ($P < 0{\cdot}0001$), direct spread of tumour ($P < 0{\cdot}0001$), lymph node involvement ($P < 0{\cdot}0001$), grade ($P < 0{\cdot}002$) and preoperative complications ($P < 0{\cdot}0001$). In the multivariate analysis death due to colon cancer was independently associated with disease stage ($P < 0{\cdot}0001$)

Conclusions: The present study shows disease stage is the major determinant of prognosis Further refinements of clinico-pathological stage methods may lead to the more judicious selection of patients in trials of adjuvant therapy.

Resections of colorectal adenocarcinoma recurrences: a series of 120 patients

B. Pol, J.R. Delpero, Y.P. Le Treut, J. Hardwigsen and G. Houvenaeghel *Institut Paoli-Calmettes, 232 bd de Sainte Marguerite, 13009 Marseille, France*

This retrospective study (1975–1995) analyses a series of 120 patients, 58 men and 62 women (mean age 62·7 years) in whom 144 local or locoregional recurrences (LR) of colon ($n = 56$) or rectal ($n = 64$) adenocarcinomas were resected The first recurrences were endoluminal in 31 patients and extraluminal in 89 patients: perianastomotic ($n = 74$), distal ($n = 6$), or pelviperineal ($n = 9$). Only 39 LR were symptomatic (32·5 per cent), 14 of which were diagnosed from an isolated elevation of CEA ($n = 11$) or CA 19·9 ($n = 3$) Resection was curative in 69 cases (57·5 per cent)

Twenty-six patients had one or several associated metastases: 61 resections were extended by necessity to one or several contiguous viscera; there were nine synchronous hepatic resections. Hospital mortality was 6·6 per cent (8 out of 120) and 5·5 per cent if repeated resections are taken into account, 48 patients presented one or more postoperative complications (40 per cent). One out of two patients (56 out of 120) received adjuvant treatment. Median survival was 24 months, and 53 months after curative resection. The rate of actuarial survival was 27 per cent and disease-free survival was 21 per cent at 5 years; 5-year survival after curative resection was 44 per cent and was 0 per cent at 54 months for palliative resections The prognostic factors that influenced survival were the curative character of resections, endoluminal site and being female. Multifactorial analysis using a Cox regression model showed that the curative character of resections was the most important prognostic variable To a lesser degree, being female was a predictive variable of survival. This study suggests that in the absence of other curative treatment, resection is essential for the treatment of such recurrence when possible. An improvement could come from therapeutic associations.

Coexisting morbidity and outcome in acute colonic pseudo-obstruction

F.M. Polignano*, M. Cramarossa*, A. Pezzolla*, and S. Ferraresе† *1st Surgical Clinic and †Surgical Pathophysiology, University of Bari, Italy

As the pathophysiology of acute colonic pseudo-obstruction (ACPO) is still uncertain, the records of patients with ACPO have been retrospectively reviewed to state the presence of underlying condition and illnesses and meaningfulness of prognostic factors Outcome and therapeutic options have been considered.

Materials and methods: From 1982 to 1996, 19 patients suffering from ACPO have been observed Acute dilatation of the colon without organic obstruction was the criterion for inclusion in the study. Plain abdominal X-rays findings such as massive distension of right colon (predominantly gas-filled) conserved haustral pattern, 'cutoffs' at the hepatic or splenic flexure, were considered suggestive of ACPO

Results: Coexisting morbidity and illnesses were very high as 84 per cent had underlying pathologies Associated conditions were. myocardial infarction (4) and congestive heart failure (4), electrolyte disturbance (4), pancreatic cancer (1) and acute pancreatitis (1), toxoplasmosis (1) and recovering from anterior resection of rectum (1). Diabetes, pulmonary chronic obstructive disease and neurological degenerative pathologies were also present in many patients Each patient had the sudden onset of abdominal distension with constipation and most were already hospitalized for other significant illnesses Three patients had colonoscopic decompression which was effective in two (one during laparotomy as a mechanical obstruction from a stenotic anastomosis was the preoperative suspicion for the clinical setting). Tube caecostomy was performed in 14 patients, one had exploratory laparotomy and decompression, right hemicolectomy was inevitable once Six presented splittings of seromuscular layers of the caecum. Maximum caecal diameter was 20 cm and minimum 10 cm. Mortality was 16 per cent (one patient was suffering from non-resectable pancreatic cancer, one from electrolyte disturbance, one myocardial infarction).

Conclusions: Although X-ray findings may be suggestive of ACPO, diagnosis is often confirmed only by operative reports Once ACPO has been recognized, management could be at first conservative, aiming to treat underlying conditions, and caecal diameter must be carefully monitored by repeated plain abdominal radiography. Colonoscopic decompression could be an effective procedure in the absence of any sign of peritoneal irritation. Tube caecostomy is the advocated surgical option in the presence of parietal splitting of caecum. Mode of treatment, age, caecal diameter, delay in decompression and bowel status are found to affect prognosis As four of these factors are easily controllable with early recognition and prompt appropriate treatment, mortality should be minimized.

The use of biofragmentable ring anastomosis (Valtrac®) in colorectal surgery without colonic mechanical preparation

S. Revuelta, F. Hernanz, M. Gomez-Fleitas and C. Fernandez-Escalante *University Hospital 'Marques de Valdecilla', 39008 Santander, Spain*

Aim: To evaluate the anastomosis leakage rate and the incidence of complication following the use of Valtrac® to perform colonic anastomosis in emergency surgery without mechanical bowel preparation or in elective surgery with a bad grade of cleaning bowel.

Patients and methods: Fourteen males with a mean age of 67 years, were operated on for complicated diverticulosis disease (3), colorectal neoplasia (20) and angiodisplasia (1) Technical procedures were anterior resection of rectum (4), right colectomy (3), left colectomy (13) and subtotal colectomy (4) In three cases a cholecystectomy was associated The Valtrac® device was applied in the conventional way, a seroserosa suture was used in all cases (polyglycolic acid, Dexon II as suture material).

Results: There were no operative complications, operative time was 105 min, stay in hospital was 12 days. Morbidity affected four out of 24, with prolongated ileus in two out of 24 There was clinical leakage in one out of 24 and colonic stricture in none

Conclusions: Biofragmentable ring is a good method to perform a primary anastomosis in a bowel with a bad grade of mechanical preparation, where a high rate of complication is hoped, avoiding undesirable colostomies.

Optimal timing for the closure of intestinal stomata: a retrospective study on 548 patients

K.-P. Riesener, R. Kasperk, W. Lehnen, M. Höfer, J. Braun and V. Schumpelick *Department of Surgery, Medical Faculty, University of Aachen, Pauwelsstr., 52057 Aachen, Germany*

Aim: To confirm risk factors for the development of complications following stoma closure.

Methods: A total of 548 patients with stoma closure operated on from 1972 to 1993 were evaluated for postoperative complications The long study period was divided into three parts according to the operative and perioperative treatment modalities used (1972–76, 1977–85, 1986–93).

Results: The overall complication rate (mostly minor) was 48 per cent in the entire study period Wound infection (35 per cent) and fever (22 per cent) were the most common complications in either period of time, the rate was markedly lowered due to the introduction of routinely performed orthograde lavage and antibiotic prophylaxis in 1986 (14 per cent wound infections, 9 per cent fever). Independently from this the complication rate was influenced by the time period between onset and closure of the stoma. Time periods below 4 weeks and of more than 1 year showed a higher complication rate compared to the patients reoperated between 4 weeks and 1 year. In particular the rate of postoperative bowel fistulas and anastomotic complications were higher in the group of patients with early stoma closure

Conclusions: Stoma closure still has a reasonable rate of postoperative complications We recommend a standardized procedure including orthograde lavage and antibiotic prophylaxis for perioperative treatment The lowest complication rates were obtained, if stoma closure was performed between 8 and 12 weeks after the initial operation

Foreign bodies within the rectum

S. Rivas, I. Guijo, D Huerga, A. Navarro, J. Morante and R. González-Cajigal *Department of Surgery, Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Avda. de los Reyes Católicos nº 2, 28040 Madrid, Spain*

The presence of foreign bodies in the rectum may result from different reasons· diagnostic or therapeutic manoeuvres (thermometers, enema nozzles etc.), introduced by the patient in effort to reduce a rectal prolapse or to relieve constipation or itching; sometimes they are secondary to a criminal assault However, the great majority of the foreign bodies result from their introduction for the purpose of erotic stimulation. There is a great variety of these objects such as bottles, vegetables, lightbulbs, etc., as well as vibrators. We present our experience in the latest five years.

Material and methods: From 1990 to 1995 we have removed five foreign bodies and treated six rectal injuries in six male patients with mean age of 48 years. Three patients were admitted to our Hospital because lower abdominal pain combined with a recent history of an erotic practice, and three patients presented with acute abdomen. The abdominal roentgenogram revealed a foreign object within the colon in four cases.

Results: The foreign objects removed included a 16 × 6cm drinking glass, a carrot, a vase and awl. In two cases (glass and carrot) manual extraction was necessary under general anaesthesia due to the great size of the object; in the other four cases a laparotomy was performed Two perforations were found in sigmoid colon (result of the removal of a vibrator in one case, and secondary to the accidental introduction of compressed air in the rectum), an acute peritonitis without perforation at operation time with the foreign body located in the ascending colon In one patient a laparotomy was necessary in order to displace toward the rectum an impacted foreign body in the pelvis (vase). Surgical procedures included a Hartmann technique (vibrator), primary suture with diverting colostomy (compressed air) and removal of the object through a colotomy placed on the caecum and closed with primary suture (awl).

Discussion: Foreign bodies in the rectum is not an infrequent pathology in a Department of Surgery, and in the literature we can found several reports with descriptions of unusual objects introduced into the rectum, as well as different methods for their extraction Most of the patients usually reveal to the surgeon the existence and length of time of a foreign body in the rectum, although the initial history is often unreliable and seems to have been concocted by the patient for the purpose of hiding a sex-related motivation. On other occasions the patient only refers to constipation and the object is discovered in a physical examination or with X-ray Frequently the patient is drunk or under the influence of drugs The high risk of these acts is the possibility of perforation of the rectum, specially when the act is done with violence, or haemorrhage, specially with the glass objects which could produce important lacerations and haemorrhages, which then require a laparotomy. The surgeon should develop an adequate relationship with these patients and with their families, because of the embarrassment and the humiliation of the patient and the ignorance of the family about their sexual practice.

What is the main predictive factor of sphincter-saving resection for low rectal cancer: the patient or the tumour?

E. Rullier, J. Carles, C. Laurent, J. Saric and M. Parneix *Department of Digestive Surgery, Saint-André Hospital, 33075 Bordeaux, France*

Aim: Sphincter-saving resection (SSR) is now possible for some patients who have a low rectal cancer, with the same carcinological security than after an abdominoperineal resection (APR). The aim of this retrospective study was to investigate the predictive factors of sphincter-saving resection for low rectal carcinoma situated between 3 and 6cm from the anal verge.

Methods: Over a period of 10 years (1986 to 1995), 98 consecutive rectal excisions were performed for tumours with a caudal edge situated between 3 and 6cm from the anal verge. Palliative resections (five cases) and Hartmann procedures (six cases) were excluded. The study concerned itself with 87 patients: 48 SSR and 39 APR. Eleven variables able to influence the choice between SSR and APR were studied: age, sex, obesity and cardiac or pulmonary insufficiency of patients, size, height, site, fixity and Dukes stage of tumours, preoperative radiotherapy and surgeon. Univariate and multivariate analyses were performed.

Results: The sphincter-saving resection rate for curative excision of low rectal carcinoma was 55 per cent (48 out of 87). In the univariate analysis, there were two significant variables more frequently associated with SSR, tumour height ($P < 0.001$) and tumour site ($P = 0{\cdot}006$) There was an association between APR and tumour fixity which did not however reach the level of significance ($P = 0{\cdot}06$) The multivariate analysis showed that only two variables were statistically associated with the type of operation, the tumour height and the tumour fixity. SSR rate was 91 per cent, 50 per cent and 19 per cent for tumours, respectively situated between 5 and 6cm, 4–4·5cm and 3–3·5cm from the anal verge: 65 per cent (11 out of 17) of fixed tumours had an APR, versus 40 per cent (28 out of 70) of no fixed tumours.

Conclusion: Patient features (age, sex, obesity, cardiac or pulmonary insufficiency) and preoperative radiotherapy were not found to influence the type of intervention in excision of low rectal cancer The choice between SSR and APR is influenced by the tumour features; principally the height and the fixity of the tumour.

Results of a new procedure for the treatment of malignant obstruction of the left colon

J.C. Salinas, E. Tejero, J. Quintana, M.A. de Gregorio, J.M. Miguelena, A. Mainar, E. Jorge, R. Fernández, L.C. Montes and R. Lozano *Department of Surgery, 'Lozano Blesa' Hospital, University of Zaragoza, Spain*

Aim: To analyse the results obtained using a new and original procedure for the treatment of malignant obstruction of the left colon.

Methods: This procedure involves three phases. (a) The resolution of the obstruction by means of an auto-expanding metal stent placed at the site of the tumour (Wallstent of 22mm diameter and 40 or 70mm length). For this purpose, with no need for anaesthesia or analgesics and with the help of an image intensifier, interventional radiology techniques are used, occasionally complemented by endoscopy. (b) On the days following the resolution of the obstruction: recovery of the general state of the patient, study of the extent of the disease and mechanical preparation of the colon. (c) Regulated and final surgery in ideal conditions for resection and primary anastomosis (if this is not suitable, the stent may be used as definitive palliative treatment)

Patients: Sixty-one patients (44 males and 17 females) with complete intestinal obstruction caused by a tumour of the left colon or rectum were treated using this procedure. The most distant tumour from the anus was situated at 70cm, very near to the splenic angle.

Results: In 59 cases the obstruction was resolved with the stent. Usually, clinical and radiological resolution took place within 24–48h when the distension only affected the colon. In 46 cases the three phases were completed (surgical intervention took place within a mean period of 10 days), and in 13 the stent constituted definitive palliative treatment. Only two patients experienced small rectal haemorrhages after the placing of the stent, and a further two experienced moderate anorectal pain.

Conclusion: This procedure offers a new safe and efficacious option for the treatment of neoplastic colorectal obstructions.

Endoscopic technique to pass through rectal and sigmoid stenoses

L. De Salvo, F. Gianiorio, G. Borgonovo, C. Bianchi and F.P. Mattioli *Istituto di Clinica Chirurgica, Università di Genova, V. le Benedetto XV, 8, 16132 Genova, Italy*

Lower sigmoid and rectal stenoses are often seen in endoscopic practice. Endoscopic dilatation of the strictures are performed more and more frequently, but, despite the large diameter of the dilator used, it is often impossible to drive the endoscope through the stricture This is due to the irregular and inelastic profile of the stenotic bowel Furthermore the tip of the rigid rectoscopic instrument or the flexible sigmoidoscope has a rectangular profile with two right angles This kind of shape does not allow any easy penetration through the previously dilated stricture. In these cases we try to go through the stricture using a balloon dilator (Meditech Rigiflex Microvasive 18mm diameter) previously modified by cutting off and blunting the thin tip of the flexible plastic material in order to avoid perforation. This inflated dilator is kept near to the tip of the endoscope and becomes itself an oval tip of the endoscopic tool Strictures can be crossed by pushing the dilator and the instrument together A partial view of the lumen is obtained through the balloon dilator made of transparent material. In this way from January 1993 to January 1996 43 rectal strictures have been dilated with balloon or bogie dilators and then crossed with the endoscopic tool using the technique previously described Using this method we also obtained an accurate description of the stenotic bowel and its careful measurement Moreover biopsy or brushing of the lesion was performed in almost all the cases In this group of 43 patients (24 male and 19 female) with an age range from 42 to 86 years we were able to go through the stricture in 37 cases (86 per cent). In six patients this was not possible for a wide and fixed angulus formed by the bowel proximal to the stricture. Major complications such as perforation or rupture of the stricture were never seen A mild or moderate pain during the dilatation time was present in 16 patients and mild self-limiting bleeding was observed during the manoeuvre We never used this procedure in patients with known diverticular disease. We can conclude that this method is a safe and acceptable procedure to pass through rectal and lower sigmoid strictures.

Experimental and theoretical background of caecorectostomy after subtotal colectomy for familial polyposis patients

N.E. Samalavicius, V. Graziene, R. Sipavicius, A. Dukstaite and A. Sipaviciute *Department of Surgery, 'Red Cross' Hospital of Vilnius University, Zygimantu 3, 2001 Vilnius, Lithuania*

Bearing in mind the significance of the ileocaecal junction, it seems to be an attractive alternative to preserve this junction while performing a prophylactic subtotal colectomy on those patients with familial adenomatous polyposis (FAP), who have a small number of rectal polyps, and for whom ileorectostomy would otherwise be indicated An animal model was designed for this purpose. From April to June 1995 six dogs were operated on at the animal department of our university, in which caecorectostomy type of operation was performed Relaparotomy, abdominal revision and removal of anastomosis was performed at 10 days, 2, 3 and 4 weeks postoperatively. No anastomotic leaks or intraperitoneal abscesses were noted. There was wound infection in dog 3 Histological examination revealed normal healing and functional and structural changes in caecal mucosa

Conclusion: (a) Caecorectostomy proved to be a safe procedure following subtotal colectomy in the dog (b) By performing this type of operation on a patient with FAP, and organizing an adequate follow-up, colorectal cancer risk would probably not be greater than after ileorectostomy, and bowel function would be better

A novel surgical technique for the treatment of vaginal vault and rectal prolapse

S. Sokmen *Bilecik State Hospital, Department of Surgery, Bilecik 11200, Turkey*

A prolapse of the pelvic organs vexes patients because of the abundance of miseries it imposes upon them and vexes surgeons because of the equally effective but different operative procedures. In this case report, transabdominal combined reconstruction of posthysterectomy vaginal vault and rectal prolapse with polypropylene Marlex mesh repair is discussed. A third-degree vaginal vault and complete rectal prolapse developed postoperatively in a 64-year-old female patient operated on for myoma uteri. After full mobilization of the rectum, reversed T-type Marlex mesh sheet was secured to the presacral fascia and sewn to the antero-lateral aspects of vaginal vault while the edges of the sling were wrapped 270 degrees around the bowel During the 32 months of postoperative follow-up, there has been no recurrence, no faecal impaction nor any other complications related to the sling itself

There is now sufficient proof that fixation of the rectum to the sacrum has a high rate of success, with a low mortality and morbidity rate Coexistent vaginal vault prolapse may be repaired at the same time and the goals of this reconstructive surgery are two-fold: to relieve the symptoms, and to restore the anatomy and the function to normal. Abdominal presacral Marlex mesh recto-colpopexy appears to be a safe and effective method in the treatment of posthysterectomy prolapse of vaginal vault and rectum

p53 expression and other prognostic factors in submucosally invasive colorectal carcinomas

A. Sory, T. Minamoto, M. Mai, P. Misiuna, A. Dąbrowski and G. Wallner *Department of General Surgery, Medical Academy, Lublin, Poland, Department Surgery, Cancer Research Institute, Kanazawa, Japan*

Aim: Our study was designed to elucidate whether p53 overexpression correlates with the metastatic potential and other adverse prognostic factors in submucosally invasive adenocarcinomas (SIA) of the large bowel and whether determinations of p53 protein could be helpful for the decision-making in therapy of SIA (local/endoscopic resection or radical surgery)

Methods: p53 protein overexpression was examined immunohistochemically in 52 primary SIA and correlated with the gross appearance, adenomatous component, grade, depth of invasion, lymphatic/venous invasion and lymph node and/or distant metastasis in each case. Statistical comparisons were performed with 2-tailed Fisher's exact text. Significance is defined as a *P*-value of less than 0·05

Results: Results are summarized in Table 1

Variable	p53 immunoreactivity Positive	 Negative	Percentage positive	*P*-value
Gross appearance				
Type I (protruding)	11	27	29	0·0034
Type II (superficial)	11	3	79	
Adenomatous component				
Present	7	17	29	0·0964
Absent	15	13	54	
Histological grade				
Well-differentiated	3	20	31	0·0917
Moderately differentiated	13	10	57	
Degree of invasion				
Massive	12	11	52	0·2621
Non-massive	10	19	35	
Lymphatic/venous invasion				
Present	5	4	56	0·4681
Absent	17	26	40	
Metastasis				
Present	7	2	78	0·0268
Absent	15	28	35	

Conclusion: p53 overexpression in colorectal SIA is associated with the enhancement of their metastatic potential and with the superficial growth pattern as another adverse prognostic factor Patients with the p53-positive SIA should be considered among potential candidates for radical surgery

Transanal resection of rectal tumours with endoscopic microsurgery

F. Stipa, C. Farina, G. Lucandri, F. Napoli, A. Lombardi, P. Mingazzini and S. Stipa *Ist Department of Surgery, University 'La Sapienza' Rome, Italy*

Transanal resection is becoming the standard treatment for large lower rectal adenomas and early cancer of the rectum (pT_1, G_1–G_2) Transanal

Endoscopic Microsurgery (TEM) is a technique which allows resection, cauterization and suture within the rectal lumen, up to 20 cm from the anal verge.

A total of 75 patients underwent transanal resection between 1991 and 1996 (56 months). Postoperative histological examination showed 29 adenomas, 40 adenocarcinomas (13 T_1, 16 T_2, 11 T_3) and six Squamous carcinomas. The mean height of the tumour above the anal verge was 6·7 cm (range 3–14 cm).

In eight patients the peritoneal cavity was breached during the procedure. Postoperative complication rate was 14·6 per cent (11 patients), which included five bleeding, two rectovaginal fistulas, two cystitis, one rectal stenosis and one incontinence. There was no postoperative mortality. Twelve patients received postoperative radiotherapy (9 T_2, 3 T_3). Patients have been followed up for a mean duration of 24·7 (median 24, range 2–56) months Recurrence rate was 3·5 per cent (1 patient) for adenomas and 15 per cent (six patients) for adenocarcinomas (T_1 17·7 per cent, T_2 18·7 per cent, T_3 22·2 per cent).

In view of the low mortality and morbidity rates and low recurrence rate we believe that TEM is the procedure of choice for patients with large adenomas of rectum and early rectal cancer, provided strict patient selection criteria are met.

'Nerve-sparing technique' and lymphectomy in rectal cancer

D. Tarroni, D. Mascagni, P. Urciuoli, V. Di Nicola, L. Greco, C. Nwamba, N. Peparini, F.M. Di Matteo, N. Sinnona and F. Custureri *III Surgical Department, 'La Sapienza' University, Viale Regina Elena 324, 00162 Rome, Italy*

The extension that should be given to lateral lymphadenectomy in the surgical treatment of extraperitoneal rectal cancer has not yet been assessed because of the difficulty of realizing randomized prospective clinical trials. The theoretical advantage of an extended lateral lymphadenectomy is represented by an accurate staging of the tumour in patients undergoing surgery for 'possible curative resection'; even if the high percentage (20 per cent) of pelvic node metastasis was already demonstrated, the prognostic impact of lateral lymphadenectomy was not proven until now The main disadvantage of an extened lateral disection is represented by the high incidence of urinary and sexual disfunctions. The nerve-sparing technique, when combined to pelvic lymphadenectomy, allows presentation of autonomic innervation to the pelvis. From January 1992 to June 1994, 15 patients with extraperitoneal rectal cancer underwent anterior resection and pelvic lymphadenectomy with nerve-sparing technique. Functional results were evaluated with clinical and instrumental examinations in eight patients out of 15; seven patients were excluded from the analysis of the data: two because of a short follow-up, two because they were female and three due to not being voluntary participants. This study demonstrated that nerve-sparing technique is an effective procedure that reduces the incidence of urinary and sexual disfunctions when properly performed.

Ileoanal anastomosis for ulcerative colitis: stapled or handsewn anastomosis?

P. Ténière, M. Scotté, L. Steinmetz, G. Delgallo, I. Leblanc, Y. Meunier and F. Michot *Groupe de Biochimie et Physiopathologie Digestive et Nutritionnelle et Service de Chirurgie Générale et Digestive, CHU Rouen, France*

Proctocolectomy with ileoanal anastomosis (IAA) has proved to be the most suitable surgical treatment for ulcerative colitis. Thus, a high rate of morbidity, partly attributed to anastomotic difficulties, has been observed following this procedure. Since 1992, we have performed stapled ileoanal anastomosis with eversion of the rectum according to an original procedure.[1] The aim of this study was to compare retrospectively the results of IAA in patients who had a stapled IAA with those who had a handsewn anastomosis.

From 1984 to 1994, 30 men and 22 women, with a median age of 33 years (16–60 years) have been operated on for an ulcerative colitis The anastomosis between the J pouch and the dentate line was handsewn in 33 patients (Group 1) and stapled in 19 patients (Group 2) among them four patients with a stapled IAA without a diverting ileostomy. The two groups were comparable for age, sex, mean duration of ulcerative colitis before surgery, and preoperative corticotherapy

The mean operative duration was significantly shorter in Group 2 (278 ± 60 mn *vs* 323 ± 53 mn, $P < 0{\cdot}01$). An anastomotic sinus was observed in nine patients from Group 1 and five patients from Group 2 (n.s.) but no patient required pouch removal. The mean length of hospitalization was 16 ± 8 days, not significantly different between Group 1 and Group 2. Three months after ileostomy closure, when it was initially performed, the mean number of stools per days was 6·9 ± 3 in Group 1 and 6·5 ± 7 in Group 2 (n.s.). with a mean follow-up of 27 months in Group 1 and 13 months in Group 2, the mean number of stools per day was 5·4 ± 1·9, not significantly different between Group 1 and Group 2 (5·3 ± 1·9 *vs* 5·7 ± 2). Five patients from Group 1 were incontinent, and one patient from Group 2 presented with nocturnal incontinence (n.s.).

These results are in agreement with those published in the literature.[2–4] They suggest that the stapled IAA anastomosis is a safe procedure. Eversion of the rectum simplifies total excision of the rectum and do not modify the rate of postoperative complications or long-term functional results. The stapling technique of IAA could allow the omission of the diverting ileostomy.

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Surgical management of perforating sigmoid diverticular disease with general peritonitis

K. Thaler, S. Gerö, P.G. Bull and W. Kreuzer *2nd Department of Surgery, Wilhelminenspital, Vienna, Austria*

Aim: This study reports our results following Hartmann procedure versus primary anastomosis in a selected mainly geriatric patient group with respect to risk factors and peritonitis grading.

Methods: Between 1986 and 1995, 85 patients (median age 72 years) underwent emergency surgery for perforated diverticulitis (Hinchey stage III). Fifty-five patients corresponded to ASA score IV/V The median Manheimer peritonitis index score (MPI) was 22 Primary resection was performed in 82 patients, 63 patients had a Hartmann discontinuity and in 19 patients primary anastomosis was attempted Restitution of continuity was performed in 34 patients, seven underwent laparoscopic restoration.

Results: Postoperative mortality was 32 per cent (27 out of 85) and morbidity was 54 per cent (46 out of 85). Following Hartmann's procedure, 24 per cent (15 out of 63) had surgical complications *vs* 37 per cent (seven out of 19) after primary anastomosis. Anastomotic dehiscent rate was 15 per cent (three out of 19). Mortality was significantly higher in patients with a MPI score over 22. Patients undergoing Hartmann's procedure had a significantly higher MPI score *vs* those who had primary anastomosis (24 *vs* 17) Following restoration after Hartmann's procedure mortality was 6 per cent (two out of 34) and morbidity 29 per cent (10 out of 34).

Conclusion: In the elderly and multimorbid patient with free diverticular perforation the two-stage Hartmann procedure with higher MPI score had better results compared to primary anastomosis.

The treatment of sigmoid volvulus via one-stage resection and primary anastomosis

Ü. Topaloğlu, A. Oztürk and S. Ünalmışer *Department of General Surgery, Haydarpaşa Numune Hospital, Istanbul, Turkey*

In this study, the importance of the treatment of sigmoid volvulus via one-stage resection and primary anastomosis is examined. During 1990–95 in the General Surgery Department of Haydarpaşa Numune Hospital, 62 patients who had undergone operation because of sigmoid colon volvulus were retrospectively studied. The most common complaints were abdominal pain, distension and the block on the passage of gas and faeces. Of patients, 33·8 per cent went straight to hospital only, in the first 24h. The mortality rate was 18·75 per cent for those whose symptoms lasted longer than 3 days ($P < 0{\cdot}05$). Chronic obstructive lung disease (10 per cent) and heart failure (8 per cent) were the two leading accompanying medical handicaps. All our patients had upright plain abdominal X-ray but in 5 patients the diagnosis was established by barium-contrast colon radiography. Detortion was performed in 17·7 per cent of patients in whom operations had to be terminated because of a variety of reasons. The following operations were performed. 41·9 per cent of patients sigmoid resection and primary anastomosis, 19·3 per cent of patients sigmoid resection and primary anastomosis with tube caecostomy, and 20·9 per cent of patients sigmoid resection and colostomy. Mortality rate, within the sequence above was 0 per cent, 0 per cent, 8·3 per cent, 23·1 per cent. The most common postoperative complication is incision-side infection with the rate of 19·4 per cent.

Consequently, sigmoid resection and primary anastomosis can be performed successfully in sigmoid volvulus cases. Colonic irrigation can be done in the cases with excessive faecal loading but caecostomy is not mandatory.

The management of rectal cancer by stapling technique

E. Tsochataridis, N. Baltayiannis, V. Botulas, L. Papavasiliou and G. Evangelou *2nd Department of Surgery, Nosileftikon Idryma Met. Tam. Stratou, and Army Share Fund Hospital, Monis Petraki 10, 115 21 Athens, Greece*

The purpose of this study is to present our results of low anterior resection (LAR) in rectal cancer. LAR and end-to-end anastomosis (EEA) were performed by a stapling technique using the following instruments: (a) roticulator (b) pursestring clamp (c) intraluminal stapling device. Seventy-six patients had this operation. The lowest distance of the anastomosis from the anal verge was 2·5cm. Only three prophylactic proximal temporary colostomies were performed in our cases. There were three leaks revealed during the operation, which were managed by additional stitches. There were no deaths in our cases. Postoperatively one perianastomotic pelvic abscess developed, which was managed by drainage and proximal colostomy. There were also three postoperative stenoses. They were managed successfully by dilatations. The use of this stapling technique in rectal cancer provides significant benefits to the surgeon and the patient, especially in very low tumours of the rectum. Our results compare favourably with the manual technique.

Endoscopic therapy of benign anastomotic stenosis of the colorectal region by electroincision and balloon dilatation

S. Truong, M. Jansen and V. Schumpelick *Surgical Clinic of the Rhenish-Westfalian Technical University Aachen, Pauwelsstr 30, D-52074 Aachen, Germany*

Strictures occur quite often after gastrointestinal operations involving an anastomosis. The incidence of postoperative strictures of colorectal anastomosis is about 4 per cent. Touson/Bougie treatment causes a high rate of perforation and reoccurrence.

Methods: To deal with these problems a new hydraulic balloon dilatation system made of polyurethane was developed. The barbell-like shape of the balloon withstands a pressure of 60KPa without deforming or increasing in diameter. Our therapeutic procedure includes as the first step the endoscopic electroincision of the scar tissue followed by balloon dilatation.

Results: Thirty-two patients with a severe anastomotic stenosis in the colorectal region were treated with the above-mentioned technique. The severity of symptoms directly correlates with the extent of stenosis (degree I diameter 13mm, $n = 18$, degree II diameter 7mm, $n = 10$, degree III diameter 4mm, $n = 4$). All patients with a stenosis of degree I and II were symptom-free after the endoscopic therapy. In three of the four cases the symptoms of stenosis of degree III could clinically be improved after the treatment. The average frequence of dilatation was 1·5-fold, complications such as bleeding or perforation were not registered. Animal studies explain anastomotic stenosis through an increased submucosal formation of collagen fibres followed by formation of scars in the anastomosis.

Conclusion: The efficiency of electroincision and balloon dilatation is based on an increased diameter in the anastomotic region without increased formation of new collagen fibres.

Local and regional recurrence in colorectal carcinoma: study of risk factors

D.S. De Vega, R. Martínez, F. Esteban, T. Jorgensen, A. Almeida and S. Tamames *Department of Surgery, Complutense University, San Carlos University Hospital, Madrid, Spain*

A prospective non-randomized study has been made with the aim of understanding the influence of clinical, histopathological and therapeutic factors in loco-regional recurrence of colorectal carcinoma.

Three hundred and thirty-six patients undergoing a potentially curative colorectal tumour resection were studied. Follow-up consisted of periodical patient interview, physical examination, tumour marker (CEA) and colonoscopy and echography or tomography. Fifty-four patients had isolated anastomotic, perianastomotic or pelvic recurrence. The findings of these patients were compared with those cases free of recurrence during the period of the study. χ^2 test, with Yates' adjustment and Student's t-test were used in the statistical analysis of results.

There were no statistical differences in age ($P = 0{\cdot}3236$), sex ($P = 0{\cdot}3631$), palpable tumour ($P = 0{\cdot}5213$), complicated or uncomplicated presentation ($P = 0{\cdot}6146$), preoperative CEA ($P = 0{\cdot}1832$), urgent or elective surgery ($P = 0{\cdot}8566$), primary or staged resection ($P = 0{\cdot}8404$), size of resection ($P = 0{\cdot}9424$), type of suture ($P = 0{\cdot}9835$), operative blood transfusion ($P = 0{\cdot}9920$), site ($P = 0{\cdot}1506$) or grade of tumour ($P = 0{\cdot}4221$) or coadjuvant therapy ($P = 0{\cdot}4050$). Distal clearance margin ($P = 0{\cdot}0049$), depth of invasion ($P = 0{\cdot}0312$), lymph node spread ($P = 0{\cdot}0036$), number of positive nodes ($P = 0{\cdot}0035$) and staging classification had statistical significance.

Pathological analysis of low rectal malignancy and preservation of anal sphincter

B. Vekic, D. Radovanovic, J. Kalaba and A. Bajec *KBC, Surgical Clinic, Milana Tepica 1, Belgrade, Yugoslavia*

Aim: In this study we analysed pathologically the specimens from 43 low rectal malignancy patients (tumour within 6cm of anal sphincter). All of them had Miles resection.

Method: The invasion of anal sphincter had no relation to the involvement of the rectal circumference, nor to the size of tumour. On the contrary, anal sphincter invasion was related to the distance from tumour to ano-cutaneous line and tumour differentiation.

Result: In 27 patients with tumours 0–3cm from anal sphincter, the sphincter was affected in 11 patients. Sixteen patients had tumours 3·1–6cm from ano-cutaneous line, and the sphincter was not affected ($P < 0{\cdot}01$). All tumours were adenocarcinomas; 16 patients had well differentiated tumours, eight poorly differentiated and three middle differentiated tumours.

Conclusion: Our results suggest that if we can have well differentiated tumours, 4–6cm from the ano-cutaneous line, an anal-saving operation can be performed.

Laparoscopic colectomy for cancer

M. Vertruyen*, G.B. Cadière*, J. Himpens*, J. Bruyns* and J.C. Lempert† **Department of GI Surgery, †Department of Gastroenterology, CHU Saint-Pierre, Brussels, Belgium*

Patient and method: Between March 1992 and September 1995, a series of 57 non-consecutive patients (24 male, 33 females) underwent laparoscopic colectomy for cancer by our group. Exclusion criteria were: obesity, large tumour volume, absence of cleavage planes on CT, history of major abdominal surgery. Average age was 66 years (range 23–86 years). Procedures were: 17 sigmoidectomies (30 per cent), 17 anterior rectum resections (30 per cent), five left hemicolectomies (8 per cent), nine right hemicolectomies (16 per cent) and nine abdominoperineal rectum resections (16 per cent) Laparoscopic operative technique was performed with respect to the following rules: stability and airtightness of the trocars, vascular control first, minimal mobilization of the tumour (no touch technique), minimal lavage of the abdominal cavity and immediate re-aspiration of the fluid, abdominal wall protection while extracting the specimen, haemostasis of all wounds in the abdominal wall. Before starting this series, all surgeons had gained good experience in laparoscopic procedures in general and in laparoscopic colectomy for benign disease in particular.

Results: Operative time ranged between 60 and 360 min (median 200 min). There were four peroperative complications (7 per cent): a perforation of small bowel sutured laparoscopically, a tumour rupture while extracting the specimen, a peroperative bleeding controlled laparoscopically and a retroperitoneal haematoma caused by the Veres needle. In five cases (9 per cent), conversion to laparotomy was performed: in three cases because of the absence of a plane of cleavage for the duodenum, the small bowel and the pelvic floor, respectively; in one case because of excessive tumour volume and in one case because of massive intraperitoneal contamination by China ink used for tattooing the lesion colonoscopically the evening before surgery Staging of the tumours was as follows: 12 Dukes A (21 per cent), 16 Dukes B (28 per cent), 18 Dukes C (32 per cent) and 11 Dukes D (19 per cent), median of number of harvested nodes was five (range 0–15). Retrospective analysis of the number of nodes harvested in 20 consecutive open colonic and rectal resections for cancer in our institution revealed an identical number

All resection margins were free of disease. One patient died of septicaemia on postoperative day 15 because of anastomotic dehiscence. Median follow up at this time is 13 months (range 0–37 months) Global survival rate (all stages included) is 67 per cent. Survival rate without evidence of disease is 60 per cent. Two patients (3 5 per cent) presented multiple tumour recurrences, notably in trocar sites. The first case was a 62-year-old patient after a left-sided colectomy for Dukes D She also had a history of right colectomy by laparotomy for cancer Multiple parietal recurrences appeared on the sixth postoperative month. They were located in the trocar sites and in the minilaparotomy scar. The second case is a 66-year-old female patient. She underwent sigmoidectomy for adenocarcinoma staged as Dukes B. Liver metastasis and multiple trocar site recurrences appeared in the second postoperative month. Aggravating factors in these two latter procedures were: laceration of small bowel in the first case and none in the second.

Conclusions: Colectomy for cancer is feasible in an oncologically acceptable fashion. Our global survival rate and disease-free survival rate are comparable with the results by laparotomy However, our follow-up is still too short and procludes long-lasting conclusions.

Gluteus maximus flap for persistent rectal fistule due to anastomotic dehiscence

T. Yalti, O. Krand and I. Titiz *Haydarpaşa Teaching Hospital, Haydarpaşa Numune Hastanesi, Uskudar, Istanbul, Turkey*

Although Miles' abdominoperineal resection still remains the 'gold standard' for the treatment of low rectal neoplasms, restorative resection may now be possible with equivalent oncological disease control and survival Abdominotrans-sphincteric resection of the rectum described by York Mason is one of the treatment alternatives for low-lying rectal neoplasms ensuring good functional results without impairing the patient's life expectancy. However, anastomic leak rate can be quite high at this type of very low anastomosis, especially in patients in whom a diverting colostomy or ileostomy has not been used. Anastomotic sepsis and faecal fistula are among the more serious concerns in the postoperative period and are usually treated by abdominal drainage and proximal diversion. In the majority of patients with anastomotic leak, spontaneous closure of the dehiscence occurs at the protection of a proximal diversion usually with a period of 3 months. However, in some the leak may never completely heal and surgical reconstruction is required. Re-resection is the generally advised method in persistent faecal fistulas. Re-resection and restoration of the intestinal continuity at a level below levator ani with hope of good anorectal function can be impossible.

Between April 1994 and April 1996, three cases developed persistent rectal fistulas that had openings on the sacral incisions following abdominotrans-sphincteric rectum resection performed at Haydarpaşa Teaching Hospital. All the cases were managed by closure of the gap at the rectal wall with a portion of advanced right gluteus maximum muscle harvested from its insertion at the fifth sacral vertebrae following generous debridement of the fibrotic edges. One month later, as the proctoscopic evaluation of the patients revealed complete closure of the fistulas with healthy colonic mucosa advanced on without any stricture, the diverting stomas were closed. The ability to bring a new source of blood supply to an ischaemic wound has tremendously improved wound healing in difficult areas Muscle flaps were demonstrated to be able to control bacterial load. Gluteal myocutaneous or solely muscle flaps are considered and used for persistent perineal sinuses following rectum amputation. Excision of the lower aspect of the gluteus maximum results in no functional deficit and as far as the blood supply is not disturbed, the flap successfully fills up the cavity and results in complete healing.

In the highlights of surgical aspects of flaps and wound healing, gluteus maximus muscle flaps were successfully used for closure of persistent faecal fistulas in these cases. When a persistent rectal anastomotic leak at the protection of a proximal diversion is encountered, closure of the fistula by a muscle flap that can deliver adequate oxygen to healing wound may be considered before a re-resectional surgery is attempted.

Changes of tendency of rectal surgery

I. Zöllei, Á. Balogh, and G. Lázár *Surgical Department of Szent-Györgyi A, Medical University, Szeged, Hungary*

Previously abdominoperineal rectal resections have been performed because of rectal cancers in 60 per cent of cases. During the last decade the tendency had changed due to excellent circular staplers. Nowadays the rate of anterior rectal resections is higher than the rate of rectal exstirpations.

The distribution of their elective radical rectal operations from 1 January 1986 to 31 December 1995 are presented. These 10 years were divided into two periods (Table 1).

	1986–1990		1991–1995		Total
Abdominoperineal rectal resection	104	55 per cent	64	42·1 per cent	168
Anterior rectal resection	85	45 per cent	88	57 9 per cent	173
Total	189	100 per cent	152	100·0 per cent	341

The tendency is clear. The rate of anterior rectal resections is improved from 45 per cent to 57·9 per cent and the rate of rectal exstirpation decreased at the same time Stapling anastomoses are recently more popular than the hand-sewn anastomoses. These were performed in 80 per cent of cases. Only three colostomies for protections of suture-line were performed, using per anum catheters as partial protection. The total mortality rate did not change significantly during the two periods. More local recurrences were found, unfortunately, in the second period. It is suggested that postoperative adjuvant radiotherapy in stadium Dukes C reduces the rate of local failures

Initial steps in colorectal stapling

V. Zykas, R. Šiugžda and D. Venskutonis *2nd Clinic of Surgery, Kaunas Medical Academy, Kaunas, Lithuania*

The creation of new surgical equipment and apparatus has enabled the performance of qualitatively more effective operations One of the preconditions of rectum operational surgery development is the usage of staples in coloproctology The first stapled rectal operations were started in our Clinic in 1968, and modern staplers have been used in coloproctology since 1993. Sixty-four patients were operated on, 47 suffering from rectal carcinoma, diverticular disease, polyposis, ulcerative colitis. Stapled anterior resections were carried out in 47 patients (73·4 per cent) between September 1993 and December 1995 Double stapling was used in 16 cases and single stapling in 31. The EEA, CEEA, (CEEAPremium) staplers were used for circular anastomoses. The double stapling group included three patients who had had ileal J pouches. The in-hospital mortality was 1/47 (2·1 per cent). One patient died of sepsis and anastomotic leakage. There were four (8·4 per cent) symptomatic and three (6·3 per cent) asymptomatic leaks giving a total leak rate of seven (14·7 per cent). The incidence was similar after double and single stapling. Three patients developed stenoses (6·3 per cent), one after double and two after single stapling.

After first 47 stapling operations for rectum carcinoma our conclusions are that staple technique offers certain advantages over traditional methods: the anastomosis is technically easier, bowel segments of different diameters can be easily anastomosed, there is significantly less contamination. The double stapling technique is a definite improvement in performance of low rectal anastomosis and permits more sphincter-saving resections

Endocrine

Frequency of malignancy in nodular thyroid disease

M. Athanasiou, S. Prigouris, S. Stylogiannis, C. Kontaxis, P. Markidis, L. Iosephidis, G. Simatos, G. Micros and J. Poulantzas *4th Surgical Department, 'Evangelismos' Hospital, 45–47 Ypsilantou Str, Athens, Greece*

The aim of this study is to identify the incidence of malignancy in patients who were operated on for solitary nodule of the thyroid or multinodular goitre.

Between January 1979 and December 1993, 472 patients were operated on for solitary nodule or multinodular goitre. The indication for surgery was based on clinical examination, ultrasonography, scintiscan, fine-needle aspiration cytology and thyroid function tests. Cases were classified in those with solitary nodules and those with multinodular goitre according to clinical examination, ultrasonography, scintiscan were confirmed by the histological examination of the specimens.

There were 399 women and 73 men (female:male 5·45·1) Solitary nodule was found in 311 cases and multinodular goitre in 161 cases Malignancy was found in 14·5 per cent patients with solitary nodule and in 15·5 per cent of patients with multinodular goitre. The percentage of malignancy in female patients less than 40 years of age was higher in the solitary nodule group than in the multinodular goitre group (22·2 per cent *vs* 12·5 per cent, $P < 0{\cdot}05$). Regarding the histological type, there were papillary in 51·5 per cent, follicular in 20 per cent, mixed papillary and follicular in 15·7 per cent, myeloid in 10 per cent and anaplastic in 2·8 per cent.

In conclusion the incidence of malignancy is similar in both solitary nodules and multinodular goitre. We identified a high risk group of female patients less than 40 years of age with solitary nodules.

Results of surgical treatment for differentiated thyroid carcinoma

D. Bordos, C. Caloghera, M. Miclaus and G. Dumitrasciuc
2nd Surgical Clinic, University of Medicine and Pharmacy, Timisoara, Romania

Aim: To evaluate the early and late results of our therapeutic approach in patients with differentiated carcinoma, which is strongly related to the stage of the disease and to the risk group of the patient

Patients and methods: Records of 123 unselected patients with differentiated thyroid carcinoma operated on from 1971 to 1995 were retrospectively analysed The histological type of carcinoma was· follicular in 44 patients (36 per cent of cases), papillary in 38 patients (31 per cent of cases) and mixed, papillary and follicular in 41 patients (33 per cent of cases). In the low-risk group (AMES criteria) there were 80 patients (65 per cent of cases); near total lobectomy on the side of the lesion and subtotal lobectomy on the contralateral side was done. The high-risk group included 43 patients (35 per cent of cases); total lobectomy on the side of tumour and contralateral subtotal or near total lobectomy was the operation of choice. Thyroid suppression and radioactive ablation were added. The postoperative morbidity rate was 24 per cent (30 patients) and the postoperative mortality rate was 4·0 per cent (five patients). The 10-year survival rate was 95 per cent (76 cases) in the low-risk group of patients and 60 per cent (25 cases) in the high-risk group. The recurrence rate of the disease was 7·3 per cent (nine patients).

Conclusions: These data indicate that this quite conservative surgical approach used at our institution has similar results to the more extensive surgical treatment used in other institutions.

Monolateral adrenal hyperplasia as a cause of primary aldosteronism

M. Bezzi, L. Angelini, M. Coppola, E. Eleuteri, M. Chiarot, V. Papaspyropoulos and N. Martone *IV Department of Surgery, University of Rome 'La Sapienza', Rome, Italy*

Primary hyperaldosteronism (PH) is due in 55–70 per cent of cases to (sometimes bilateral) adrenal adenoma. In other patients, if we exclude rare cases of carcinoma or familial hyperplasia, it is usually idiopathic as it is due to bilateral hyperplasia. More recently another cause of PH has been pointed out: adrenal unilateral hyperplasia with micronodular and macronodular pathological findings of which only 20 cases have been reported.

Materials and methods: We have examined two cases: a woman of 63 years old and a man of 42 years old. Both suffered from arterial drug-resistant hypertension with cephalea, acouphony, vertigo, tachycardia and arrhythmia

		Patient 1		Patient 2	
Pressure		170/97	140/90	155/100	130/80
Potassium		4·04	4·80	2·87	3·90
Aldosterone	cl	160	Norm	238	Norm
pg/ml	ort	284	Norm	405	Norm
PRA	cl	0·2	Norm	0·3	Norm
ng/ml/h	ort	0·5	Norm	0·5	Norm

Conclusions: The diagnostics possibilities of these rare forms of hyperplasia are represented by NMR, angioCT and adrenal phlebography with selective sampling from adrenal veins for the study of separate secretion of aldosterone and PRA. Only in this way we can demonstrate the unilateral morphofunctional hyperplasia characterized by a response to adrenalectomy similar to adenoma. Endocrine characteristics of these patients and the response to surgical therapy leave, for the time being, the discussion of a new syndrome rather than an adrenal dysplasia developing adenoma unanswered.

CO_2 retropneumoperitoneum under coelioscopic control for renal and adrenal surgery

L. de Canniere, L. Michel, F. Lorge and A. Rosiere *Mont-Godinne University Hospital, Yvoir, B-5530, Belgium*

Purpose: After gaining expertise with direct CO_2 insufflation of the retroperitoneal space on an animal model. we describe in the videotape the details of our videoscopic posterior approach to the retroperitoneal space.

Methods: Patients are placed in the lateral decubitus position. A posterior Veress needle is introduced in the lumbar triangle and the retroperitoneal space is then insufflated progressively with CO_2 (Pr 12mmHg) Development of the retropneumoperitoneum is watched by a camera inserted via an intraperitoneal subcostal trocar. The retroperitoneal space created by the retropneumoperitoneum can easily be widened by blunt dissection with a 10-mm diameter coaxial laparoscope inserted through a trocar placed in the lumbar triangle. Under intra- and extraperitoneal control, another three 10mm retroperitoneal trocars are then introduced without injuring the peritoneal layers. The pneumoperitoneum is then exsufflated in order to allow the retropneumoperitoneum to enlarge further

Results: This technique that provides a convenient working space was applied to 10 patients who underwent 11 surgical procedures (three adrenalectomies, five nephrectomies, two renal tumorectomies and one cystectomy). For two adrenalectomies, extraperitoneal approach was easily extended to a combined coelioscopic approach Increase of $PaCO_2$

above 43 mmHg was recorded in five patients. There were no complications.

Conclusion: Both approaches, laparoscopic and retroperitoneoscopic, are complementary. This technique is bloodless and atraumatic.

Surgical treatment of hyperparathyroidism: our experience in the last 25 years

E. Castillo, R. Palasí, S. Bonafé, J.L. Ponce and S Sancho-Fornos *University Hospital 'La Fe', Avenida de Campanar 21, 46009-Valencia, Spain*

Introduction: This study aims to analyse all the cases of hyperparathyroidism (HPTH) with surgical treatment in our Service in the last 25 years in detail: epidemiology, histopathology, clinical classification (primary or secondary to renal disease) and surgical technique

Patients and methods: From 1970 to 1995, 160 patients with diagnosis of hyperparathyroidism were operated on: 4 per cent in the context of a syndrome of multiple endocrine neoplasia; 63 per cent primary hyperparathyroidism, 33 per cent hyperparathyroidism secondary to chronic renal insufficiency (7 per cent after renal transplantation), 66 per cent women and 34 per cent men The most frequent initial symptoms in the primary HPTH were renal colic by recurrent renal stones, and subsequent epigastric pain, arterial hypertension, duodenal ulcer and arthritis syndrome. The most constant alteration in biochemistry is the hypercalcaemia confirmed by the Parfitt formula. An adenoma is the most frequent histopathology finding followed by hyperplasia

The surgical technique most often used was subtotal hyperparathyroidectomy in the cases of hyperplasia, whereas in the patients with adenoma the surgical intervention applied was tumour excision, and for the remainder the identification of parathyroids (with peroperative biopsy in those cases that were macroscopically affected). Cryopreservation was systematically applied in cases of hyperplasia

In general the postoperative hypocalcaema was minor in the primary HPTH, the most frequent symptoms being peribuccal and hand parasthesia. Treatment with oral calcium was given in a small percentage for a period between discharge and first outpatient medical control. In HPTH secondary to renal disease the hypocalcaemia was more severe Reinterventions were required in the 8 per cent with recurrent hypercalcaemia.

There were two cases of permanent hypocalcaema. In one, with association of primary HPTH + thyroid papillary carcinoma in which total thyroidectomy was achieved, and the second by subtotal parathyroidectomy for hyperplasia There were four cases of pronounced HPTH with calcium levels over 20 mg/dl, requiring urgent intervention in one case

Conclusions: Hypocalcaemia is the most frequent complication in postoperative HPTH, being more severe in the cases of HPTH secondary to renal insufficiency. In the case of subtotal parathyroidectomy after renal transplantation, the evolution of the postoperative hypocalcaemia is different.

Surgical treatment for hyperparathyroidism

A. Catania, V. D'Andrea, S. Sorrenti, L. Falvo, G. Lippolis, F.M. Di Matteo, F. Biancari and E. De Antoni *3rd Department of General Surgery, University 'La Sapienza', Policlinico Umberto I, Viale Regina Elena, 324-00161 Rome, Italy*

We evaluated the results of 144 patients who have been operated on for hyperparathyroidism. One hundred and ten patients had primary hyperparathyroidism and 34 patients had secondary hyperparathyroidism. Preoperative localization by ultrasonography was attempted in all cases, while only a few patients were preoperatively evaluated by arteriography and selected venous sampling for parathyroid hormone concentration. After surgical resection for primary hyperparathyroidism, transient postoperative hypoparathyroidism occurred in 41 patients (28 per cent), recurrent disease occurred in three patients (2 per cent), while one patient experienced persistent hyperparathyroidism (0·7 per cent) In three cases (2·1 per cent), resection of solitary adenoma and biopsy of all parathyroid glands resulted in permanent hypoparathyroidism that required long-term administration of vitamin D and oral calcium. Neither recurrent nor persistent hyperparathyroidism occurred in patients surgically treated for secondary hyperparathyroidism, and no patient experienced postoperative hypoparathyroidism Because it has not yet been demonstrated that preoperative studies may improve parathyroid localization or cure rate of initial cervical exploration, we emphasize the importance of an adequate surgical strategy and a diligent search for parathyroid glands in the neck region for treatment of this challenging disease.

Prospective randomized trial comparing efficacy and safety of three fibrin glues on haemostasis in large thyroid surgery

A. Courtade[*], A. Brogniez[†], B. Carnaille[†], N. Grandjean[‡], P. Duval[‡], J.J. Huart[§] and C. Provet[†] [*]*Digestive and General Surgery,* [†]*General and Endocrinologic Surgery, University Hospital, 59037 Lille,* [‡]*LFB, 91958 Les Ulis,* [§]*CRTS, 59012 Lille, France*

Local use of fibrin glue (FG) is common in surgery to complete local haemostasis. Biocol (LFB) is an FG-containing human thrombin and fibrinogen with bovine aprotinin (Ap, 3000 KUI/ml) as antifibrinolytic agent (ATF). Ap has been replaced by synthetic ATF, tranexamic acid (AMCA) The aim of this study was to evaluate its efficacy and safety in large thyroid surgery

Patients and methods: Three groups (Group 1, Group 2, Group 3) of patients, receiving an FG, in which only ATF differed, were compared (Group 1 = Ap 3000 KUI/ml; Group 2 = AMCA 10 mg/ml, Group 3 = NaCl 0·9 per cent) It was a double-blind prospective randomized trial Patients had to be between 18 and 65 years old, without blood-coagulation abnormalities or other local haemostatic medication. They had to be operated on a sub-total or total thyroidectomy for goitre >50 g. After thyroidectomy and classic surgical haemostasis, a spray of 5 ml of FG was applied on each thyroid lodge, before double drainage Criteria of postoperative assessment were volume of drainage at 6 and 24 h; overall volume of drainage (OV) and clinical tolerance Statistical analysis used Student's *t*-test or Wilcoxon tests according to normality of groups for inter-group analysis, and Kruskal–Wallis test for overall analysis

Results: Between August 1994 and January 1996, 87 patients were included in this trial (Group 1 = 30, Group 2= 29, Group 3 = 28). There were 20 toxic and 67 non-toxic goitres. Groups were comparable at the inclusion Overall and inter-group analyses are presented in the following table.

Variables	G1	G2	G3	Overall	G1 *vs* G3	G2 *vs* G3	G1 *vs* G2
6 h (ml)	36 ± 28	26 ± 16	53 ± 30	*P* < 0·001	*P* = 0·01	*P* < 0·001	n s
24 h (ml)	78 ± 67	67 ± 36	105 ± 45	*P* = 0·003	*P* = 0·009	*P* < 0·001	n s
OV (ml)	125 ± 72	106 ± 44	161 ± 66	*P* = 0·005	*P* = 0·04	*P* < 0·001	n s

Clinical tolerance was comparable between the three groups. Local adverse events were nine cervical abscesses (three/group), one post-operative bleeding and one suppurative scar (Groups 1).

Conclusions: Replacement of Ap by AMCA 10 mg/ml, as Biocol (LFB) FG is effective in large thyroid surgery. This confirms previous experimental studies.[1]

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Clinical and biochemical changes after surgery for morbid obesity

F. De la Cruz, G. Ortega, J.I. Martínez, S. González, J.M. Menéndez, J. De la Cruz, P. Yuste and C. Pérez *General and Digestive Surgery Service 'A', '12 de Octubre' Hospital, Complutense University, Madrid, Spain*

Introduction: Bariatric surgery not only reduces weight and decreases body self-image disparagement in severely obese patients but also contributes to improve their life expectancy by means of ameliorating certain related medical problems and biochemical abnormalities

Patients and methods: Since 1986, 58 severely obese patients (50 women, 8 men) have been operated on by our group. The surgical procedures used were Roux-en-Y gastric bypass ($n = 11$), vertical banded gastroplasty ($n = 12$) and silastic ring gastroplasty ($n = 35$). No operative mortality is reported. Mean age was 39·6 years. Preoperative average weight 130 kg, average height 159·7 cm, overweight 69 kg (115 per cent) and ideal body weight 60·2 kg.

Results: Bariatric surgery ameliorates respiratory insufficiency (16 per cent to 0 per cent) and shortness of breath (59 per cent to 2 per cent). Pickwickian syndrome (sleep apnoea syndrome and obesity hypoventilation syndrome), ankle swelling and varicose vein disease disappear during the first year. The frequency of menstrual irregularities also diminishes after surgery (37 to 19 per cent). We found a significant fall in blood glucose levels (172 mg/dl to 117 mg/dl) Triglycerides and uric acid levels reverted to normal after surgery (168 mg/dl to 91·2 mg/dl and 6·1 mg/dl to 4·3 mg/dl, respectively) There is a minimal but real fall in haemoglobin, haematocrit and folic acid blood serum levels. Cholesterol, iron, vitamin B12 and total protein serum levels remain stable after surgery.

Conclusions: Surgical treatment of morbid obesity ameliorates pulmonary and circulatory problems, as well as certain biochemical parameters in these patients, thus contributing to a better quality of life and a prolonged life expectancy.

Monitoring of blood sugar and serum insulin level during insulinoma surgery

K. Darvas, P. Antony-Móré, I. Irtó, M. Tarjányi, J. Horányi and L. Flautner *1st Surgical Department of Semmelweis Medical University, Budapest, Hungary*

Insulinoma is one of the causes of hypoglycaemia and hyperinsulinism The diagnosis and localization of the tumour can be difficult and after a long preoperative period the operation solves the endocrine problem Before the operation the patients are treated with glucagon or diazoxid to normalize the blood sugar and serum insulin state.

We reviewed 25 patients operated on for insulinoma Three types of general anaesthesia were applied: halothane-fentanyl for nine patients, isoflurane-fentanyl for 10 cases and propofol-fentanyl anaesthesia for six patients. The blood sugar level, the serum Na, K, Mg, Ca levels were monitored, the acid-base balances were controlled and in 14 patients the serum insulin levels were detected during the anaesthesia. During the operation 5 per cent glucose infusions were given till the tumour extraction and after it was continued with 0·9 per cent saline infusion. After the extraction of the tumour the blood sugar levels increased from 4·2 mmol/l to 5·1 mmol/l and the serum insulin level decreased from 45 uU/ml to 31 uU/ml. For two patients with malignant insulinomas the serum insulin level did not decrease after the operation, the average level was 65 uU/ml Metabolic acidosis was seen in three patients in the halothane anaesthesia group. The serum electrolyte level remained in the normal range The principal challenge during anaesthesia for surgical excision of insulinoma is to monitor serum glucose and insulin level and maintenance of a normal blood glucose concentration Propofol and isoflurane anaesthesia is preferable.

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Papillary thyroid cancer: can metastasis be predictable?

M. Düren, F. Öz, H. Akı, Y. Bükey and A. Özyeğin
Cerrahpaşa Medical Faculty, Istanbul, Turkey

Which pathological features of a papillary thyroid cancer (PTC) are of interest to the clinician to predict possible cervical lymph node metastases (CLNM)? Paraffin blocks of 214 patients (173 women, 41 men) who have been diagnosed as having PTC with CLNM between 1980–1990 have been reviewed retrospectively The parameters analysed were diameter, capsule of the tumour, growth pattern (lobular, infiltrative), pleomorphism, nuclear polarity, cellular type, necrosis, lymphocytic infiltration, follicular component, clear nucleus and DNA content.

The classic subgroup of PTC with a diameter >2 cm in male patients with pleomorphism, prismatic cell type and necrosis showed a higher incidence of CLNM. The occult PTC with a diameter >0·5 cm, without a capsule showing pleomorphism and prismatic cell type had a higher incidence of CLNM. The follicular variant with pleomorphism, lobular and infiltrative growth pattern had a higher incidence of CLNM. These parameters can help both the pathologist and the clinician to evaluate a present tumour according to a possible CLNM and modify the clinical follow-up method.

Prognostic value of interactive computerized morphometry in mortality and recurrence of papillary thyroid carcinoma

J.E Pérez Folqués, S. Sancho-Fornos, J.A. Botella, J. Del Pino, J. Pertusa and M. Hernández *Department of Surgery, Hospital University 'La Fe', Valencia, Spain*

Introduction: The objective of this research is to evaluate interactive computerized morphometry (ICM) as prognosis factor in mortality and recurrence of papillary thyroid carcinoma.

Patients and methods: The prognostic factors for papillary thyroid carcinoma were analysed in a series of 86 surgically treated patients with a mean follow-up 12·3 years. Clinical, surgical, pathological and morphometric data were assessed, obtaining geometric and densitometric parameters of the cell nucleus (area, perimeter, diameter, form factor, optical density and optical integrate density), by digital analysis of the image 'IBAS 2000 ZEISS/KONTRON'. The survival curves were analysed according to the Kaplan–Meier method and multivariate analysis included the Cox regression models.

Results: The 5-year survival rate for papillary thyroid cancer was 90 per cent and 10-year survival was 82 per cent. The factors that showed prognostic significance for survival were the patient's age, distant metastasis, histological type, tumour size and nuclear area. Regional nodal metastases and nuclear perimeter played a role in the disease-free survival rate.

Conclusion: In summary, our study indicates that morphometry analysis significantly contributes valuable information to papillary thyroid carcinoma prognosis, which cannot be obtained by standard methods.

Different behaviour of metastatic differentiated thyroid carcinoma between patients with metastases at diagnosis and later metastases

E. Gemar, T. Fernandez Cuadrado, J.A. Baena, S. Obiols, M. Vidal, C. Ruiz and J. Mesa *Surgery and Endocrinology Units, Hospital General Vall d'Hebron, Barcelona, Spain*

Purpose: To evaluate whether there is a different prognosis between patients with differentiated thyroid carcinoma (DTC) with local or distant metastases at diagnosis (Initial: I) and those who developed them later in the follow-up (late. L), and its relationship to known prognostic factors, ^{131}I uptake and thyroglobulin (Tg) levels.

Methods: Forty-one out of 234 patients had metastatic DTC. We saw 39 extrathyroidal neck involvement (I 39; L 25). Metastases: lung 39 (I 18; L

21), bone 11 (I 18, L 21), skin 3 (I 2, L 1), brain 2 (L), mediastinum 1 (L) They were all treated with near total thyroidectomy and ablative doses of ^{131}I. Metastatic disease was treated with radiodine when ^{131}I uptake was positive and/or surgery when possible. We have considered as prognostic factors age at diagnosis, initial extension of the disease and histological type. We have evaluated the sensibility of ^{131}I uptake and Tg measurements in the detection of metastatic DTC Statistics: Student's *t*-test, Fisher's test and relative risk (rr) calculation according to Mantel–Haentzel method

Results: Mortality. I 15/40 (37 per cent); L 28/55 (51 per cent) Positive ^{131}I uptake: I 38/40 (95 per cent); L 40/55 (73 per cent). Tg > 10ng/ml: I 37/37 (100 per cent); L 35/47 (75 per cent) Age and histologic type. patients with metastatic papillar carcinoma at diagnosis were younger than those who developed metastases later (21 ± 22 *vs* 48 ± 18 years; $P <$ 0·05) but the former have had a better prognosis than the latter (mortality I 5/17; L 4/8) However, deceased patients were older than alive (55 ± 14 *vs* 35 ± 18 years, $P <$ 0·05). In follicular carcinoma, there were no differences between the age in group I and L (63 ± 15 *vs* 53 ± 17, P = n s). However, in group L (n = 6) all patients died and in group I 7 out of 17 patients died. Patients in group L have a mortality rr of 12·1, compared with the rest of patients, but if we calculate the rr for older than 40 years of age, it results 7·6. However, after adjusting for age, the rr in group L is 5·5.

Conclusions: (a) Patients with metastases at diagnosis have a better prognosis than those who developed them later This feature could be related to a younger age in papillary carcinoma but not in follicular carcinoma. After adjusting rr for age, this feature remains true. (b) The sensitivity of ^{131}I uptake and thyroglobulin measurements in the detection of metastatic DTC is greater in the group with metastases at diagnosis than in the later group This could reflect the dedifferentiation process that some patients experienced in their follow-up.

Total thyroidectomy in the treatment of benign multifocal nodular thyropathies: why is this the therapy of choice?

L Giacomelli, A. Pulcini, G. Fabrizio, E. Gagliarducci, C. Porcelli, A.V. Granai, A. Manno, R. Gabatel, R. Finizio, L Minocchi, E. Gallinacci and F. Stio *VI Surgical Department, Rome University 'La Sapienza', Viale Regina Elena, 324-00161 Rome, Italy*

Aim: To stress the role of total thyroidectomy (TT) in the therapy of benign multifocal nodular goitre

Patients and methods: From 1986 to 1995 we operated on 278 patients, for benign thyroid disease; no intraoperative death occurred. The overall rate of complications was 4·5 per cent (eight cases) and in particular two haemorrhages (1·1 per cent of cases), one permanent hypocalcaemia (0·5 per cent of cases), three temporary hypocalcaemias (1·7 per cent of cases) with return to normal calcium levels within 4 months from the operation. Histological examination showed eight cases of carcinoma (seven papillary and one follicular carcinoma)

We believe that benign multifocal nodular goitre is to be considered as a lesion which involves the entire gland, the 'nodule' has to be considered therefore only as a sign and the pathogenesis of this complex condition is to be found not only in the thyroid stimulating hormone (TSH) but also in insulin, insulin-like growth factor-1 (IGF-1) and epidermal growth factor (EGF) Many authors consider TT the therapy of choice only in cases of neoplastic lesion firstly because of the high rate of complications connected with this kind of operation. As a matter of fact, a recent review of the literature showed that the rate of lesions to recurrent laryngeal nerves during TT is more or less the same (0·4 per cent of cases) than those reported subtotal thyroidectomy (ST). The same can be said regarding permanent hypoparathyroidism (TT = 0·14 per cent of cases, ST = 0·15–4·3 per cent of cases). On the other hand, the complication rate is much higher during operation for relapse after ST We must also take care of the possibility of a sporadic carcinoma in a nodular multifocal goitre: in this case the TT allows removal of all the possible neoplastic foci, also allowing an easier follow-up of the patient The surgical option of preserving a part of the gland not modifying the endocrine balance, does not always give good results In many cases hormonal secretion by the residual gland is not sufficient to reach a condition of euthyroidism and hormonal therapy is to be given; TT allows a better and easier follow-up (physiological hormonal serum levels). The residual gland can also develop a relapse, with an incidence rate ranging from 3 per cent to 55 per cent in the different series and this rate seems not to be reduced by hormonal therapy.

Conclusions: On the basis of such considerations, the authors believe that TT is the therapy of choice in the treatment of the benign nodular multifocal goitre, because it is the only option able to stop the natural history of the disease and it is as safe as more conservative surgical approaches in terms of complications.

Decreased extrathyroidal tri-iodothyronine production in non-thyroidal illness: benefit or harm?

Z.H. Gündoğdu, D. Akaydin and G. Hergenç *Faculty of Medicine, Department of Paediatric Surgery and Biochemistry, Kocaeli University, Turkey*

A low serum T3 level is exceedingly common in patients with non-thyroidal illness. A reduction in extrathyroidal conversion of T4 to T3 resulting from reduced activity of T4 5'-monodeiodinase enzyme is the most important factor underlying this phenomenon, other factors include reduced serum binding of T3 and a dampening of the pituitary-thyroid axis. Several recent studies have addressed the question of the significance of lowering of serum T3 in systemic illness. However, no study has previously reported the effect of surgical illness results and electrolyte imbalance on thyroid function in children In our study 24 children, who have electrolyte imbalance related to surgical illness of whom 10 female (42 per cent) and 14 male (58 per cent) with 13 (54 per cent) being younger than six years of age were evaluated with control group of 12 children. Daily blood-samples were taken, total serum T3, T4 and rT3 concentrations were measured by specific radioimmunoassays. Although all patients were clinically euthyroid, 70 per cent had serum T3 values in the hypothyroid range, less than 0·8ngr/ml. The mean serum T3 of the sick patients 0·68 ± 0·25ng/ml was significantly less than that of control patients, 1·07 ± 0·25ng/ml. Serum T4 levels were comparable to those of control patients and serum TSH was not significantly increased in the same group of patients. In our study we found normal serum T4 levels The mean serum T4 of the sick patients 7·75 μg/100 ml was near to control patients 9·79 μg/100 ml. 3,3',5'-triiodothyronine increased where serum T3 production is decreased thus this study shows that rT3 is a potent inhibitor of peripheral conversion of T4 to T3.

As a result, despite the absence of thyroid disease, paediatric patients with surgical non-thyroidal illness frequently have changes in serum thyroid hormone measurements that may suggest frequent drops mainly because of a decrease in the rate of T3 production from T4. Since T3 is the major active thyroid hormone, it is surprising that patients with decreased serum T3 do not appear hypothyroid The decrease in serum T3 is probably an adaptive change to non-thyroidal illness, the clinical impression of euthyroidism is supported by the finding of a normal serum TSH level in most patients

Surgical treatment and diagnosis problems in pheocromocytoma

G. Ionescu, A. Maghiar, C. Pop, S. Ionescu, T. Maghiar and A. Stancu *Surgical Clinic II, University of Oradea, 5 Armatei Romane St, Oradea 3700, Romania*

The paper deals with diagnosis and therapeutic behaviour problems in pheocromocytoma. The study reviews 44 patients, with a total of 50 pheocromocytomas, operated on during 1960–1994 Their distribution according to sex presents a slight increase in females and ages ranged between 17 and 65 years old The investigations concerned the biological diagnosis, considered always as a priority and the topographic localization of the tumour.

The pre-surgical preparation was done by a team with special emphasis on the adrenergic receptor blockade The approach was initially retroperitoneal but subsequently a transabdominal approach was introduced systematically. The post-surgical results were good in 43 patients for whom the clinical and biological signs disappeared. There was only one death, of a patient with a malignant pheocromocytoma.

In conclusion we can affirm that given a biological and topographic diagnosis, surgical therapy can be very good for the patient if all the pre-surgical treatment and surveillance conditions are satisfied

Indications for the operative treatment of adrenal tumours 'incidentaloma'

K. Kołomecki*, J. Narębski*, H. Kołodziej-Maciejewska†, K. Kuzdak*, M. Bartos*, L. Pomorski* and G. Strózyk* *Clinic of Surgery and †Clinic of Endocrinology, *Institute of Endocrinology, Medical University of Łódź, ul. Pabicnicka 62, 93-913 Łódź, Poland*

The aim of the study is to evaluate indications for operative treatment of non-functioning adrenal tumour type 'incidentaloma'

Up to May 1996, 11 operations on adrenal 'incidentaloma' tumours were conducted at the Clinic of Surgery. In the course of preoperative investigation the exact location of an adrenal tumour was determined in most cases but only a little information on its histological nature was provided. On the basis of a fine-needle biopsy malignancy was suspected in only two cases. Aspirates were often taken from the neighbouring organs e.g. the spleen. All tumours were operable. The results of postoperative histological examination were as follows: hamartoma, CA clarocellulare, schwannoma malignum, immunocytoma, organised adrenal haemorrhage, hypotrophy (two cases) and carcinoma (three cases) of the suprarenal gland, highly malignant phaeochromocytoma (one case) The diameter of the tumours ranged from 1 to 15 cm and it is worth noticing that smaller diameters were typical for malignant tumours The patients after adrenalectomy experienced no serious postoperative complications. Among the 'incidentaloma' tumours, three (27 per cent) were benign and the others malignant We succeeded in removing all these tumours within the healthy tissues. At various survival periods the patients have reported feeling well. Up to now, no patient has died and no complications have developed.

Due to the frequent occurrence of malignancy in 'incidentalomas' their quickest removal, improving a prognosis, is justifiable Adrenalectomy therefore, seems to be indicated for all patients in whom such tumours are diagnosed.

Total thyroidectomy or lobectomy in benign nodular disease of the thyroid: changing trend in surgery

N. Korun*, C. Aşcı*, H. Duman*, T. Yılmazlar*, E. Tuncel† and E. Ertürk† *Department of Surgery, †Department of Endocrinology, Uludağ University School of Medicine, Bursa, Turkey*

In a period of 23 months (January 1994–December 1995) 344 thyroid surgery was performed for benign disorders after fine-needle aspiration (FNA). Among these 55 total thyroidectomy or lobectomies were evaluated. Mean age was 43·6 ± 9·7 and female:male ratio was 47:8 (5·8) All the cases were operated by the consensus of the surgery + endocrinology + pathology council according to a protocol based on the FNA, thyroid function tests, scintigraphy and ultrasound. Suspect FNA or suspect nodules during the surgery were verified by frozen section

Among the 55 cases benign nodules, seven (13 per cent) had bilateral total, and 48 (87 per cent) unilateral lobectomies were performed. Postoperatively three cases (5·8 per cent) of seroma, one transient hypoparathyroidism (1·8 per cent) and one unilateral vocal cord paralysis (1·8 per cent) were seen as complications.

In our centre the FNA cytology had been a routine procedure since 1992. Surgery for benign thyroid disease is reduced 50 per cent since then. This study was started after 2 years of the FNA procedure We knew from the literature residual nodules are the most common cause of recurrence in nodular thyroid disease, so some cases should need radical surgery when they are scheduled for operation. Morbidity of surgery for recurrent disease is unacceptably high compared with lifelong supplement therapy.

Changes in bone mass and serum markers of bone metabolism after parathyroidectomy

A. Kristoffersson*, R. Lorentzon† and K. Thorsen† *Departments of *Surgery and †Orthopedics, Sports Medicine Unit, University Hospital of Northern Sweden, Umeå, Sweden*

Today bone symptoms are uncommon in patients with primary hyperparathyroidism (HPT). The possibility of subclinical bone involvement is however still important and reduced bone density is an indication for surgery.[1] In this study we present the results of the long-term effects of surgery on bone mass, serum markers of collagen metabolism as well as on bone-specific alkaline phosphatase and osteocalcin.

Material and methods: Twelve women with HPT and 12 sex- and age-matched controls were investigated. Body mass density and bone mineral content (BMD, BMC) were determined preoperatively and after 3, 6, 12 and 23 months by means of dual-energy X-ray absorptiometry Total body, whole spine and proximal femur measurements were made. In addition, changes in serum parathyroid hormone (PTH) bone specific alkaline phosphatase (B-ALP), osteocalcin (OC), C-terminal propeptide of type I procollagen (PICP) and the immunoreactive C-terminal telopeptide of type I collagen (ICTP) were analysed comparing preoperative status and results at 23 months.

Results: A significant increase in BMD of the whole spine ($P < 0\cdot05$), femoral neck ($P < 0\cdot05$), Ward's triangle ($P < 0\cdot05$) and trochanter region was noticed after 23 months. PTH, B-ALP and OC were strongly correlated preoperatively. The serum levels of PICP and ICTP did not differ *vs* the control group preoperatively and no significant changes occurred after operation.

Conclusions: This study supports that bone mass is significantly improved after surgery in patients with HPT. B-ALP and OC are markers of bone involvement in HPT while the clinical usefulness of serum markers of collagen metabolism in the long-term follow up after surgery seems limited. We advocate a liberal approach towards surgery in patients with HPT

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Pre-clinical Cushing's syndrome in patients with incidental adenomas

C. Letizia*, G. De Toma†, R. Massa‡, S. Cerci*, A. De Ciocchis*, S. Coassin*, C. D'Ambrosio* and D. Scavo* *I Patologia Medica, †I Clinica Chirurgica and ‡Radiologia, University of Rome, Italy*

Adrenal tumours are usually diagnosed by clinical symptoms of hormone excess. The increasing use of ultrasound and computed tomography results in the detection of a substantial number of incidentally discovered adrenal tumours (INC).

Of 24 consecutive patients with INC, recruited between 1993 and 1995, (nine males, 15 females, mean age 54·7 ± 13·6 years), 13 (54 per cent) were adrenalectomized and in five patients the INC was left in place. The size of the INC was 3·6 ± 2·1 cm (mean ± s.d.)

Pre-clinical Cushing's Syndrome was detected in seven (29 per cent) patients with INC (overnight dexamethasone suppression test and the accumulation of radiocholesterol have been used to characterize the function of adrenal cortical lesions) and in all a benign adrenal adenoma was removed. No patients developed adrenal insufficiency after removal adrenal adenoma. In two patients with positive MIBG-scinti-scan and slight augments of plasma catecholamines adrenalectomy disclosed a benign adrenal adenoma The remaining adrenalectomized patients presented: adrenal hyperplasia (2), adrenal carcinoma (1) and teratoma (1).

In conclusion, we suggest that all patients with adrenal masses be studied with the overnight dexamethasone suppression test and with scintigraphy for identifying an adenoma autonomously secretes glucocorticoid hormones and in these patients we recommend adrenalectomy as the treatment of choice.

Completion thyroidectomy as a second operation in the treatment of differentiated thyroid cancer

G.L. Lukács*, F. Gyory*, S. Szakáll† and G. Balázs* *1st Department of Surgery and †Institute of Pathology, Medical University Debrecen, H-4012 Debrecen P.O. Box 27, Hungary

Background: The role of elective completion thyroidectomy after unilateral operation for differentiated thyroid carcinoma has been widely debated. Its use as a routine procedure is restricted by the increased morbidity rate of reintervention The aim of the present work is to determine the indications and the assessment of the surgical results.
Methods: In a 15-year period (1979–1993) 87 completion thyroidectomies were performed within 6 months from the initial intervention in our Institute. This group represents 25 per cent of a total of 346 patients who were operated on, during the same time interval, for differentiated thyroid cancer (253 papillary and 93 follicular). The initial operation of 43 patients was performed at other institutes Out of the 87 patients, 53 suffered from papillary, 34 from follicular carcinomas, and the diameter of tumours exceeded 1·5 cm Another group of 54 patients was treated surgically with lobectomy + isthmectomy, despite intra- or postoperative diagnosis of carcinoma. Completion thyroidectomy was not performed.
Results: The reoperative specimens contained residual tumour in 24 patients (28 per cent). There was no difference according to histological types and the decisive factors were tumour size, multicentricity, invasiveness. The postoperative complications were. transient recurrent nerve palsy in 13 cases (15 per cent), permanent recurrent nerve palsy in eight cases (9 per cent), tetany in two cases (2 per cent) Patients not undergoing completion thyroidectomy developed tumour (one case), cervical lymph node recurrence (two cases), distant (bone) metastasis (one case). One unilateral recurrent nerve injury occurred, but no hypoparathyroidism developed.
Conclusions: Total thyroidectomy with completion saves nearly one-third of 'high-risk' patients with tumours exceeding 1·5 cm from residual carcinoma Performed with appropriate care it involves low morbidity. For encapsulated minimally invasive carcinomas the operation of choice remains lobectomy + isthmectomy.

The use of ^{99m}Tc-Tetrofosmin/^{99m}Tc-Pertechnetate in the diagnosis of parathyroid adenomas: preliminary report with a new technique

J. Malamitsi*, A. Manouras†, C. Nikolaou†, N. Apostolidis†, C. Proukakis* and B. Golematis† *Department of Nuclear Medicine and †First Department of Propaedeutic Surgery, Athens University Medical School, Hippocration Hospital, 114 Vas. Sophias Ave., GR-115 27 Athens, Greece

Exact localization of parathyroid adenomas (PTA) is necessary for defining anatomic diagnosis. Many studies have been proposed with various success and occasionally more than two are required. For the preoperative localization of PTA in seven patients with clinical hyperparathyroidism (after conventional study with ultrasound and computed tomography) i.v. ^{99m}Tc-Tetrafosmin (a radionucleotide used for functional imaging of myocardium) was used Front neck images were taken at 15 min and at 2–3 h postinfusion. On a separate day, ^{99m}Tc-Pertechnetate was used and thyroid scan was done. Comparison evaluation of early and late images with ^{99m}Tc-Pertechnetate was done. Focus with increased uptake of ^{99m}Tc-Tetrofosmin but not obviously in the thyroid scan was considered as PTA. The followed operation confirmed the diagnosis in all cases (100 per cent accuracy). Mean operative time was 48 min (32–75 min) including intraoperative frozen section in comparison with 69 min (41–139 min) in a series of 21 patients before the application of this new technique. Exact preoperative localization will be proved beneficial in minimizing the number of surgical re-interventions by putative imaging of ectopic adenomas as well as minimizing significantly the operative time.

Total thyroidectomy in the treatment of benign thyroid diseases

M. Marchesi, M. Biffoni, F. Tartaglia, G. Nuccio, F. Stocco, M. Jaus and F.P. Campana General Surgery, University of Rome 'La Sapienza', Italy, Policlinico Umberto I, Viale Regina Elena 324, 00161 Rome, Italy

The aim of this study is to demonstrate the suitability and the safety of total thyroidectomy in the treatment of benign thyroid diseases. A total of 492 total thyroidectomies were performed from 1986 to 1996 for multinodular goitre, Graves' disease and chronic thyroiditis (169 lobectomies for monolateral nodular goitre were also performed). All the patients were studied with ultrasonography of the neck, T_3, T_4 radioimmunoassays, ^{131}I scan All the thyroidectomies were performed by the same surgeons. Thyroidectomy was always performed with the identification and preservation of the whole cervical tract of the recurrent laryngeal nerve, the parathyroid glands were visualized where possible and their vascular supply was also preserved. In all patients the serum calcium level was measured before the operation and at the second and third days postoperatively All the patients underwent a control of laryngeal motility before and after the intervention. There were no incidences of permanent recurrent laryngeal nerve palsy or permanent hypoparathyroidism (none out of 492 total thyroidectomies and none out of 169 lobectomies), temporary recurrent laryngeal nerve palsy occurred in three patients after total thyroidectomy (3 out of 492 = 0·6 per cent) and in one patient after lobectomy (one out of 169 = 0·6 per cent). Temporary sub-clinical hypocalcaemia occurred in 133 patients treated by total thyroidectomy (133 out of 492 = 27 per cent), with clinical manifestation in 13 patients (13 out of 492 = 2·6 per cent). At present, our results demonstrate that total thyroidectomy does not increase the specific morbidity of thyroid surgery and prevents the nodular recurrences, that are seen in the thyroid remnant after subtotal excision as far as 30 per cent in the literature.

Radical surgery of the adrenal carcinoma with wide en-bloc tumour resection

C. Di Martino, P. Celestre, A. Conti, M. Iacampo, N. Caruso, A. Civitella and F. Cristini Ospedale di Colleferro, Usl Roma G. Divisione di Chirurgia, 00034 Rome, Italy

Surgical treatment of adrenal cortical carcinoma is usually far from a standard procedure because of its rare incidence, its difficult diagnosis, and its frequent locally extensive invasion to adjacent structures due to its high malignancy. Moreover, radiation as well as chemotherapy has been used with more favourable results in patients where surgical treatment was highly radical. Therefore aggressive surgery with, if necessary, complete wide en-bloc resection of peri-tumoral structures and organs remains the only possible therapy to prolong survival, as well as repeated debulking operations in the case of tumour recurrence This is why frequent organ removal has been reported in association with primary tumour excision, when alone it is not effective, such as nephrectomy, splenectomy, liver or pancreatic partial resection, in order to obtain resectability of primary tumour and to provide radical therapy. The authors report the case of a 53-year-old female patient suffering from recurrent intestinal obstruction due to the presence of a retroperitoneal mass, 20 × 15 cm in size, extending from the superior pole of the kidney to the iliac bone and including the spleen and the left colon as shown by CT scan. At laparotomy a large retroperitoneal mass infiltrating the pancreatic tail and the splenic hilum was observed. Resection of the mass was obtained through a wide en-bloc resection of the tumour with distal pancreatectomy and splenectomy The histological report was carcinoma of the adrenal cortex. At 1 year after the intervention the patient is alive and well The reported case confirms observations by other authors about the necessity of a wide resection of the tumour and the adjacent structures and organs in the case of giant adrenal carcinoma to obtain prolonged survival in these patients

Tertiary hyperparathyroidism in hypophosphataemic rickets

R. Palasí, E. Castillo, J.L. Ponce, S. Bonafé, and S. Sancho-Fornos *Department of General Surgery, Hospital 'La Fe', Av. Campanar 21, 46009 Valencia, Spain*

Introduction: Hypophosphataemic rickets involves two defects; impaired proximal tubular reabsorption of phosphate and a relative deficiency of 1,25-dyhydroxycholecalciforol (vitamin D) production We report on the development of tertiary hyperparathyroidism in a male of 10 years old, treated for familial hypophosphatemic rickets with high doses of phosphate and vitamin D.

Case report: A 10-year-old male presented with manifestations of growth failure, bowing of the legs and olympic front. Laboratory study results showed hypophosphataemia (<3mg/dl), normal serum calcium and increased alkaline phosphatase increased (>500U/L). Radiography showed osteomalacia, overall osteoporosis in lower limbs and other rachitic bone changes. With clinical, analytical and radiographic features we diagnosed a familial hypophosphataemic rickets. Since diagnosis in 1988 the patient has been continuously treated over 7 years with oral phosphate and vitamin D The patient's symptoms improved and hypercalcaemia (14mg/dl) developed with an increase of serum level of PTH (76pg/ml). With these results we thought about the possibility of a tertiary hyperparathyroidism, and diagnostic procedures were done. Echography showed all the glands to be abnormal and nodular and in the gammagraphy with Ta-Tc showed hyperplasia of superior and inferior glands in both sides. With diagnosis of tertiary hyperparathyroidism, parathyroidectomy was performed and the right and left superior glands, right interior and one-third of the left inferior gland were removed After parathyroidectomy the serum level of calcium decreased to 9mg/dl and serum level of PTH was 2·5pg/dl.

Conclusions: Long-term administration of therapeutic phosphate supplements induce secondary hyperparathyroidism that eventually becomes autonomous or tertiary. The development of tertiary hyperparathyroidism is a non-reversible situation by medical treatment and needs surgical resolution.

Postoperative complications in thyroid neoplastic disease

S. Di Paola, L. Persico Stella, A. Napoleoni, M. Di Domenica and G. Pagano *General Surgery Division, 'S. Giuseppe' Hospital A, USL RM H Albano Laziale, Rome, Italy*

The total excision of the thyroid gland because of neoplasia may force the surgeon to sacrifice the adjacent structures. In our General Surgery Division 201 patients have undergone an operation on the thyroid gland 187 were affected by a benign pathology and 14 by neoplastic pathology Of the latter, 10 were papillary carcinoma, three were follicular carcinoma and one was a metastasis of a previous renal carcinoma. In six patients we found a postoperative hypocalcaemia; in three cases the blood calcium reached a normal value within the first 48h and did not require any therapeutic intervention, while in the other three patients we found a permanent postoperative hypoparathyroidism, and hence the need for specific therapies. In one case we found a bilateral recurrent laryngeal nerve palsy, due not to a direct injury of the two nervous branches but to an excessive preparation of them because of the extracapsular extension of the neoplasia together with a vascular invasion The patient has had a tracheostomy and has been sent to an otorhinolaryngology department for an operation on the vocal chords In our experience we have not met any case of lesion of the superior laryngeal nerve We conclude that total thyroidectomy operations for neoplasia often make it necessary to sacrifice structures that are adjacent to the gland in order to obtain a radical excision. This often implies postoperative consequences for the patient that can be a major handicap.

Papillary microcarcinoma of the thyroid gland: is it a benign disease?

E. Martin-Perez, E. Larrañaga and P.A. Serrano *Hospital la Princesa, Department of Surgery, C/ Diego de León 62, Madrid, Spain*

The purpose of this study has been to evaluate our results in the diagnosis, treatment and outcome of patients with papillary microcarcinoma of the thyroid.

Methods: We retrospectively reviewed 37 patients with papillary microcarcinoma of the thyroid gland who underwent surgery in the last 20 years. Age, sex, size and type of growth, presence or absence of lymph nodes and distant metastases, associated benign thyroid disease, surgical treatment and follow-up were reviewed. The mean follow-up was 10 years

Results: Of 37 patients, 32 (87 per cent) were women (mean age 50 years; range 16–66 years) and 5 (14 per cent) men (mean age 51·8 years; range 21–78 years). The average diameter of the tumours was 0·7cm. All had papillary structures present. Associated benign thyroid disease was: goitre 13 (35 per cent), adenoma 6 (16 per cent), hyperparathyroidism 3 (8 per cent), chronic thyroiditis 1 (3 per cent), Graves' disease 1 (3 per cent). Ten (27 per cent) patients presented as cervical adenopathy without a palpable mass. Fine-needle aspiration cytology detected papillary carcinoma in 10 (27 per cent) patients. Fourteen (38 per cent) patients had cervical lymph node metastases, four (11 per cent) had distant metastases to lung and one (3 per cent) patient had both pulmonary and bone metastases Seven (19 per cent) patients had multifocal thyroid disease. In five (14 per cent) cases, there was capsular invasion. All 37 patients underwent surgical treatment: total thyroidectomy with node dissection in 28 (75 per cent) and unilateral in nine (24 per cent). Thirty-three patients (89 per cent) were free of tumour at the end of the study, and four tumours recurred. Three patients died from recurrent disease and one patient with lung metastasis is free of disease after 5 years.

Conclusions: The absence of a thyroid mass, or other abnormalities, in several tests does not exclude an occult papillary carcinoma of the thyroid with metastases. For most of patients, we suggest aggressive surgical treatment. Aspiration cytology can detect a virtually occult papillary carcinoma that will require patients to have surgery. These results demonstrate the malignant potential of the tumour.

Medullary thyroid carcinoma in multiple endocrine neoplasia type IIB

J.C. García Pérez, J. Calatayud, L. Díez Valladares, M. Maestro, L. Izquierdo, A. Sánchez-Pernaute, A.J. Torres and J.L. Balibrea *II Department of Surgery, Hospital Universitario San Carlos, C/ Martín Lagos s/n, 28040-Madrid, Spain*

Introduction: Medullary thyroid carcinoma (MTC) constitutes 5 per cent of all thyroid carcinomas. It is characterized by a non-follicular sheetlike histological pattern, an extracellular deposition of amyloid, and a high incidence of lymph node (48 per cent) and distant (38 per cent) metastases. It can present as a sporadic neoplasm (non-familial) or as a familial tumour (non MEN MTC), or associated to other endocrinopathies (MEN IIa and MEN IIb). Both hereditary diseases are inherited as autosomal dominant traits, although either (and more often MEN IIb) may occur sporadically as a genetic mutant We report a case of a patient with an MTC included in a MEN IIb syndrome.

Case Report: The patient is a 12-year-old girl, studied since she was 17 months old because of different bone diseases From 2 years old she had been under the lowest weight percentile, and suffered from diarrhoea. The physical examination revealed a Marfanoid constitution, with narrow forehead, micrognathia, Byzantine arch hard palate, small dental arcade, large ears with low implantation, thick lips and multiple mucosal neutromas in the tongue. The thyroid gland was palpable and slightly enlarged. Bilateral cervical lymphadenopathy was also present. The blood analysis, calcium, phosphate and total protein measures were within normal ranges T4: 0·93, TSH: 2·69, antithyroid antibodies· negative, calcitonin: 1124pg/

ml (normal under 30 pg/ml), CEA: 22·3 ng/ml, 25HD3: 21 ng/ml, vanillylmandelic acid· 6·56 mg/24 h, urine metanephrines. 0·70 mg/24 h, urine catecholamines adrenaline 13·28 µg/24 h, norepinephrine 22·56 µg/24 h, dopamine 243·8 µg/24 h, PTH i: 40 pg/ml. A biomolecular analysis using the restriction enzyme FokI found a mutation in the exon 16 (2684) of the RET protooncogen. A thoracoabdominal CT showed no adrenal masses The cervical ultrasound showed bilateral thyroid nodules Total body scintigraphy with MIBG found no anomalous uptake The thyroid nodules were needled, and cells compatible with medullary thyroid carcinoma were found. The patient was prepared for surgery. A cervical anterior transverse incision was performed The left prethyroid muscles were infiltrated by a thyroid mass The thyroid gland was not enlarged, but showed multiple bilateral hard nodules. The trachea and oesophagus were also infiltrated All parathyroid glands except for the right lower were quite enlarged. A total bilateral thyroidectomy and subtotal parathyroidectomy, followed by resection of a portion of the oesophageal wall, resection of prethyroid muscles and radical modified bilateral lymphadenectomy and upper mediastinal lymphadenectomy were performed. One quarter of one parathyroid gland was preserved and the rest were cryopreserved. Both recurrent laryngeal nerves were also preserved. In the immediate postoperative period the patient suffered tetany that needed treatment with intravenous calcium and intramuscular vitamin D3. She was also treated with 100 µg/day of L-thyroxin The pathological studies confirmed the presence of a multicentric medullar thyroid carcinoma with multiple lymph node invasion and esophageal infiltration. The postoperative calcitonin level was 200 pg/ml

Commentary: Williams and Pollock in 1966 observed the association of MTC, phaeochromocytoma, multiple mucosal neuroma, ganglioneuromatosis and a characteristic physical appearance. Usually there is no parathyroid affectation. Diagnosis can be made upon the phenotype at an early age or even at birth. It is imperative that patients with MEN IIb be treated early by total thyrodectomy plus lymphadenectomy since the MTC in this setting is much more aggressive than in patients with MEN IIa or sporadic MTC.

Concurrent hyperthyroidism and thyroid carcinoma: report of four cases

T. Ratia, I. Lasa, E. Tobaruela, A. Rodriguez, A. Gutierrez, F. Hernández Merlo, M. Díez, J.M. Enriquez, J. Alvarez and J. Granell *Departments of Surgery and Endocrinology, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain*

Introduction: The relationship between hyperthyroidism due to Grave's disease (GD) or toxic nodular goitre (TNG) and thyroid carcinoma remains uncertain Widely differing frequencies of this coincidence have been reported: 0·76 per cent–8·7 per cent Most of the cases are occult carcinomas, and few are suspected preoperatively. Thyroid stimulating hormone (TSH) stimulates growth of thyroid cancer cell via signal transduction pathways: adenylate cyclase and phospholipase C Activating mutations of the genes coding for TSH receptor have been found in many hot nodules Increased response to TSH is probably due to an over expression of the gene for the TSH receptor as it occurs in some thyroid cancers. In GD a disturbance of the immune surveillance system leads to the production of thyroid-stimulating autoantibodies against TSH receptors, resulting in enlargement and hyperfunction of the gland.

Material: A retrospective study of 48 cases of thyroid cancer operated between 1989 and 1995 in our Institution showed the coexistence of hyperthyroidism in four female patients. 2 GDs (aged 21 years and 40 years) and two TNGs (aged 48 years and 20 years). All patients received antithyroid drugs, and only the oldest one of the TNGs received ^{131}I preoperatively (10 mCi). The histological diagnosis was well differentiated papillary carcinoma in the four cases It was found as an incidental finding during the final microscopic evaluation of the specimen in three cases (two TNG and one GD), and it was diagnosed preoperatively in the youngest (20 years) GD through the fine-needle biopsy of a lateral enlarged metastatic lymphadenectomy A near total thyroidectomy was performed in all but three cases. A total thyroidectomy and a right modified neck dissection was performed in the case where the diagnosis of thyroid cancer was confirmed in the operating theatre. At 4 weeks after surgery a thyroid scan was performed, and there was no evidence of metastasis Ablative doses were given when the tumour size >1·5 cm in three cases. two TNGs and one GD. All patients were given oral thyroxine therapy.

Results: Transitory hypoparathyroidism was registered after one total thyroidectomy + neck dissection (GD + thyroid cancer with node metastasis), no other significant morbidity was observed No recurrence or death has been registered after a follow-up that ranged from 17 to 72 (mean 42·5) months

Conclusions: Although this association is rare, the diagnosis of hyperthyroidism does not exclude by itself a possible presence of concurrent thyroid cancer That circumstance suggests that surgery should be the preferred treatment in toxic nodulate goitre In our very short experience it seems that the oncological prognosis of differentiated thyroid cancer is not altered by the coexistence of hyperthyroidism.

Surgical management of substernal goitres

P Schroeyers, L.A. Michel, L. de Canniere and A. Rosiere *Mont-Godinne University Hospital, B-5530 Yvoir, Belgium*

From 1982 to 1995 120 patients underwent resection for substernal goitre at the University Hospital of Mont-Godinne. We and others[1,2] have chosen to refer to any goitre in which more than 50 per cent of its mass is inferior to the thoracic inlet as substernal.

The commonest presenting symptoms were neck swelling (41 per cent) and thyrotoxicity (40 per cent). Computed tomography (CT) clearly demonstrated retrosternal extension in all 105 patients who underwent this preoperative test CT of the cervico-mediastinal area was the most sensitive preoperative test

For 113 patients (94 per cent) a cervical approach was adequate for goitre resection. Seven patients required an additional sternotomy mainly for retrotracheal extension of the goitre (four), for acute respiratory distress early after bronchoscopy in a referred elderly patient not known to have a compressive goitre (one), and carcinoma of the thyroid invading the tracheal lumen (two). One of them required a total cervical exenteration with mediastinal tracheostomy according to Grillo[3] carcinoma of the thyroid was present in nine patients (8 per cent). There were no major postoperative complications or death related to the procedure.

In conclusion: the presence of substernal goitre is an indication for resection based on the potential risks of malignancy, acute respiratory distress, the high incidence of thyrotoxicity and a low surgical morbidity

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Primary hyperparathyroidism: a 5-year experience

G. Simatos, S. Prigouris, S. Stylogiannis, G. Verycocacis, G. Constantinidis, M. Athanasiou, A. Stavrou, P. Zairis and J. Poulantzas *4th Surgical Department, 'Evangelismos' Hospital, 45–47 Ypsilantou Str, Athens, Greece*

The aim of this study is to present the diagnostic approach and the outcome of the surgical management of primary hyperparathyroidism.

Between January 1989 and December 1993 28 patients (22 women and six men) underwent surgery for primary hyperparathyroidism in our unit. The mean age was 56 years (range 38–69 years). Seventeen patients had asymptomatic hypercalcaemia or non-specific symptoms such as fatigue and abdominal cramps Among the other 11 patients most common presentations were skeletal complaints and renal calculi In addition to calcium and parathormone (PTH) assays, ultrasonography, thalium-technetium scan and computed tomography were the most useful diagnostic techniques with a sensitivity of 73 per cent, 57 per cent and 25 per cent, respectively

Histological examination revealed adenoma in 18 cases (64·3 per cent), hyperplasia in seven cases (25 per cent), carcinoma in one case (3·6 per cent) and potentially malignant adenoma in two cases (7·1 per cent). All patients were followed for a mean period of 42 months Operation was successful in 24 cases (85·7 per cent). Recurrence of hyperparathyroidism was observed in three cases. In one case the adenoma was not localized. The success rate in patients with adenoma was higher than in patients with hyperplasia (88·9 per cent and 71·4 per cent, respectively)

The patient with carcinoma had normal calcium levels 2 years postoperatively. Permanent hyperparathyroidism was observed in two cases of symptomatic hyperplasia.

In conclusion modern imaging techniques achieve preoperative localization in most cases. Surgery is the definite method of treatment with high success rates in most cases.

Surgical treatment of Basedow disease: total thyroidectomy

F. Tartaglia, F. Stocco, E. Bernardini, M. Marchesi, M. Biffoni, M. Sgueglia and F P Campana *University of Rome 'La Sapienza', III Department of Surgery, Viale Regina Elena 324, 00161 Rome, Italy*

The authors report personal experience about surgical treatment of Basedow hyperthyroidism. After a short review of literature, the authors stress the medical trait of Basedow disease with possible spontaneous resolution Thus it is clear that the number of cases surgically treated is necessarily low Thirty patients, all with specific antibodies, were treated with total thyroidectomy. The therapy chosen and the results obtained are hereinafter shown, on the basis of personal experience, in the absence of definitive hypoparathyroidism and inferior laryngeal nerve injuries Thus total thyroidectomy must be the therapy of choice of Basedow disease when medical treatment is not available.

Clinical and experimental studies on hormonal tumour markers in neuroendocrine tumours

B. Wängberg, G. Westberg, O. Nilsson, G. Lindstedt and H. Ahlman *Departments of Surgery, Pathology & Clinical Chemistry, Sahlgrenska University Hospital, Göteborg, Sweden*

Optimal diagnosis, treatment and follow-up of patients with neuroendocrine tumours depend heavily on the use of reliable tumour markers. The specific hormonal products, or their metabolites, are often used, as well as general neuroendocrine cell markers, e.g chromogranins. As pharmacological treatment is often combined with surgery it is crucial to elucidate the effect of such agents on tumour marker levels. Patients with metastasized midgut carcinoid tumours undergoing surgery, ischaemic treatment of the liver and octreotide were studied regarding amine excretion and chromogranin A levels in plasma. Tumour cells from these patients were grown in long-term primary cell cultures and the intracellular levels as well as secretion of tumour products to culture media were studied. 5-HTP, 5-HT and 5-HIAA were analysed by reverse-phase HPLC, chromogranin A and tachykinins by radioimmunoassay.

In 22 per cent (14 out of 64) of patients with metastasized midgut carcinoids, surgery alone reduced 5-HIAA to normal levels (41 ± 6μmol/24h) after an observation time of 69 ± 6 months. In 40 patients with bilobar hepatic metastases, treatment with the somatostatin analogue octreotide significantly reduced the mean urinary excretion of 5-HIAA by 42 ± 9 per cent (from 726μmol/24h to 421μmol/24h) When tumour cells were studied *in vitro* a variable secretory pattern of tryptamines extra- and intracellularly was seen, indicating enzyme deficits in individual tumours. Octreotide (10^{-8}M) significantly reduced the medium levels of 5-HTP, 5-HT as well as 5-HIAA by approximately 40 per cent and in most tumours there was also a reduction of intracellular tryptamine levels. The reduction of NPK secretion parallelled that of 5-HT. The presence of MAO activity within tumour cells was confirmed immunocytochemically and by the effectiveness of MAO blockade (nialamide 10^{-6}M). In comparison with octreotide, dexamethasone (10^{-8}M) caused equipotent and additive reduction of tryptamine secretion but increased the intracellular stores The reduction of chromogranin A secretion from midgut carcinoid tumour cells was pronounced (by 65 per cent) after octreotide This contrasts to the claim that chromogranin A is a marker of tumour volume.

Conclusions: The established tumour markers of carcinoid disease are markedly influenced by pharmacological treatment modalities without corresponding effect on tumour mass. This must be considered in the follow-up of individual patients as well as in the evaluation of treatment programmes. *In vitro* data indicate that corticoids could be of value in acute octreotide-refractory carcinoid crisis, while octreotide seems better suited for long-term treatment.

A new treatment concept in airway obstructing thyroid cancer

G. Wolf*, P. Kohek*, E. Geyer†, B. Pakisch†, P. Rehak*, H. Hauser*, M. Thalhammer*, G. Schramayer* and W. Langsteger‡ **Surgical Clinic, Division of Endocrine Surgery, †Radiologic Clinic, University of Graz, Austria, ‡Hospital Barmherzige Brüder, Graz, Austria*

Palliative therapy in infiltrative non-resectable thyroid cancer is, up to now, apart from tracheostomy or stenting intraluminal and/or external radiation. A Combined Modality Treatment (CMT) was introduced, consisting of (a) surgery, (b) intraoperative radiation therapy (IORT), (c) external beam radiation (EBR), (d) brachytherapy, eventually combined with (e) intraluminal NdYg/laser disobliteration and (f) endoluminal hyperthermia (ET).

Material and methods: Five out of 155 thyroid cancers at the 1st Surgical Clinic Graz were of the poorly differentiated locally infiltrative follicular subtype entering the IORT protocol. After tumour surgery in the thyroid bed an IORT-boost of 4–10Gy was administered followed by external radiation up to 40Gy Three other patients had tracheal infiltration by advanced thyroid tumours. In these a combination of treatments were administered: endoscopic NdYg-laser surgery was performed to clear the endophytic tumour part (one session = 40W/3sec beam interval). Endotracheal brachytherapy was used with the 192-IR MicroSelectron HDR with an applicator of 2mm diameter passed through the bronchoscope (5Gy/session). External beam radiation was delivered on an outpatient basis with daily fractions of 2Gy up to 50–70Gy. Endoluminal hyperthermia was introduced as a method adapted from oesophageal cancer treatment using a modified nasogastric tube. HT was performed via 2 MA 251 interstitial applicators inserted into two lateral catheters. The interstitial mode at 915MHz for treatment and monitoring was in use.

Results: Four out of five in the IORT-protocol are tumour-free in the thyroid bed, two out of five with distant tumour spread. One out of five died of mediastinal tumour without local recurrence. Three out of three of the extended CMT protocol are tumour-free in the trachea, one out of three with pulmonary metastases in stable disease and one out of three died of aggressive tumour growth at 22 months without further tracheal stenosis.

Conclusions: The optimal palliative procedure must provide rapid and durable relief from symptoms. Combination of the various methods in advanced infiltrative thyroid cancer may be a rescue treatment avoiding low-quality palliation and/or providing a more conservative approach in surgery than tracheal/oesophageal resection.

Gastroduodenal

Complex treatment of fistulas in the upper gastrointestinal tract

K. Adamonis, S. Bradulskis, E. Brazaitis, M. Jievaltas and J. Juočas *Kaunas Clinical Hospital Nr 3, Hipodromo 13, 3002 Kaunas, Lithuania*

The purpose of present study is to analyse the results of treatment of 13 patients with postoperative fistulas of the upper gastrointestinal tract since 1990 Due to the unsatisfactory results of treatment this problem is still important in modern surgery

The essence of our method is (a) the preparation of the gastrointestinal tract and improvement of the patient's status using enteral feeding through the tube endoscopically passed beyond the opening of the fistula; (b) aspiration of the gastric and duodenum contents, (c) curretage and placement of a double lumen drain through the fistula tract; (d) reinfusion of digestive juice which leaks out of the fistula, (e) pharmacological depression of the gastric and pancreatic secretion.

It was found that using our complex treatment there were two outcomes: (a) spontaneous closing of the fistula (nine cases) and (b) endoscopic filling of the internal opening of the fistula (four cases) In all cases the fistulas healed The advantages of this method are preservation of the patient's nutritional status and healing of fistulas in an extremely short time

Factors affecting recurrences after resection for early gastric cancer: our experience

P. Aurello, G. Ramacciato, F. D'Angelo, P. Barillari, C. Cicchini, A. Stazi, A. Napolillo and A Curcio *First Department of Surgery, University 'La Sapienza', Via del Policlinico 155, 00161 Rome, Italy*

The prognosis after surgical treatment of early gastric cancer (EGC) is excellent even with node-positive disease The aim of this study is to identify the pathological features of EGC with high risk of recurrence. From 1978 to 1992 438 patients with gastric cancer underwent curative resection, 44 of these (10·0 per cent) presented EGC In 10 (22·7 per cent) tumours were limited to the mucosa, while in 34 (77·3 per cent) tumours reached the submucosal layer, lymph-node involvement was identified in 10 (nine in submucosal cancer, one in mucosal cancer) patients (22·7 per cent); 29 (65 per cent) tumours were classified as differentiated type, and 15 (35 per cent) as undifferentiated; macroscopic elevated type (I, IIa) was presented in five cases (12 per cent), depressed type (IIc, III) in 29 cases (65 per cent), and mixed type in 10 cases (23 per cent) The operative mortality rate was 4·5 per cent (two patients); two patients were lost at follow-up. Five (12·5 per cent) patients died of recurrence during follow-up period the tumour extended to the submucosal layer in all of the patients; four were staged as N1 (40 per cent), one as N0 (3 per cent), all the tumours presented as depressed macroscopic types (17·2 per cent); and, finally, three patients were affected by differentiated tumours (10·3 per cent), two patients by undifferentiated tumours (13 3 per cent). One (20 per cent) of the five patients died more than 5 years after curative resection. Thirty-five patients are alive with no evidence of disease Relapse in lymph node was apparent in four (80 per cent) patients, and blood-borne metastases in three (60 per cent) patients We conclude that submucosal invasion, lymph-node involvement, and macroscopic depressed type are associated with high risk of recurrence.

Palliative surgery in gastric cancer

J.I. Jorge Barreiro, I Capele Fernandez, J.A. Alvarez Pérez, J. Siro Pérez, R. Baldonedo Cernuda and J. Gutiérrez Fernandez *General Surgery Service, 'San Agustin' Hospital, Camino de Heros, 4. 33400 Avilés, Asturias, Spain*

Palliative gastric cancer surgery is intended to relieve the patients of symptoms with an acceptable morbi-mortality rate In the years 1980–94, we have diagnosed 530 gastric carcinomas, 477 (89·8 per cent) of which underwent surgery, with resection in 363 (76·3 per cent). In 58 (16·3 per cent) of them the procedure was considered as palliative surgery due to persistence of a residual macroscopic tumour in abdominal area, such as liver, peritoneal or ganglionar metastasis.

Twenty-six of these cases were located as a tumour at the fundus, six at the cardia, four in a gastric remnant and 10 were generalized. The surgical techniques used were either partial gastrectomy in 35 cases or total gastrectomy in 23 cases. The post-surgery morbility rate was 31·7 per cent and the mortality rate was 10·4 per cent, less than that of definitive surgery, 12·4 per cent. The survival rate was 6 2 months for palliative surgery *vs* 4·3 months for gastric bypass and 3·6 months for laparotomy The average stay was 17·2 and 15·2 days for the palliative surgery and definitive surgery, respectively

Conclusions: Palliative surgery in gastric cancer is indicated for relief of pseudo-ulcerous symptoms, not just for stenosis The mortality is acceptable at 10·4 per cent. The immediate survival is higher than that of definitive surgery.

The role of *Helicobacter pylori* in dyspeptic complaints after bilateral truncal vagotomy + pyloroplasty

N. Baruk, C Yıldırım, M. Can, T. Ceran and Ş. Gokgoz *Cumhuriyet University General Hospital, Department of General Surgery, Sivas, Turkey*

In this study the role of *Helicobacter pylori* in dyspeptic complaints in patients who had undergone BTV + P surgery due to duodenal ulcer have been investigated. The study has included a total of 60 patients, 30 patients had dyspeptic complaints (study group) and 30 patients were without complaints (control group) All the patients were examined by gastroscopy and biopsies were taken *H. pylori* has been looked for in all biopsies The mean age of the study group was 53·5 years, and of control group was 52·5 years. Female/male ratios were 6/24 and 5/25, respectively. While no *H pylori* was found in the control group, it was found to be as 45 per cent in the study group ($P < 0\ 001$). A triple therapy of bismuth + amoxycillin + oxidazol were performed on patients with *H pylori* (+) and 96 per cent eradication was maintained. After eradication 62 per cent of the *H. pylori* (+) patients have shown clinical recovery Histopathological change did not take place This study makes us think that *H pylori* could be an important factor in dyspeptic complaints after BTV + P

Non-Hodgkin's gastrointestinal lymphomas

P.L. Bianchi, G. Mezzetti, M. Varriale, M. Mele, S Arcieri, F M. Di Matteo, N. Peparini, A.M. Romani, D Mascagni and A. Filippini *III Surgical Department, 'La Sapienza', University, Rome, Italy*

Introduction: Non-Hodgkin's Lymphomas (NHL) of the gastrointestinal tract represent 60 per cent of all extranodal lymphomas NHL amount to 1–7 per cent of all gastric malignant neoplasms, 18–20 per cent of all small

bowel neoplasms and 0·2–1·8 per cent of colorectal neoplasms. It is commonly accepted that they originate from the lymphoid tissue in the submucosa, from lymphocytes, plasma cells and lymphoid nodules in the lamina propria or from intraepithelial lymphocytes. The last two are a part of the so-called MALT which is a tissue that has evolved to protect the freely permeable surface of the gastrointestinal tract and other mucosal membranes directly exposed to the external environment.
Methods: The authors have observed in the period between 1982 and May 1996 19 patients affected by gastrointestinal non-Hodgkin's lymphoma Seven of them were males and 12 females; mean age was 57 years (range 22–71 years) The stomach was involved in 16 cases, the small bowel alone in two cases. In one female patient there was the coexistence of a gastric and jejunal localization. In each case the criteria of Dawson excluding generalized NHL were fulfilled. All the patients were stratified using the Ann Arbor method modified by Schmidt-Vollmer.
Results: Seven patients were at stage I, five at stage II1, three at stage II2 and four patients were at stage IV. For 11 cases a follow-up of between 1 and 72 months is available. Nine patients are alive and disease-free. Two patients died: one 27 months after surgery, the other at 14 months. Both had been operated on for a high-grade IV stage gastric NHL. The authors would like to stress the importance of surgery as first line therapy in the treatment of gastrointestinal NHL

Early gastric cancer: our experience

C. Bosi, G. Mariani, M Andreoli and R. Buzzacchi *Division of General Surgery, Ospedale di Ostiglia, Italy*

The number of early gastric cancers (EGC) EGC in the north-western countries and the USA is about 10 per cent the whole amount of stomach cancers and is known to differ considerably from the number found in the eastern countries (about 50 per cent). This can be easily accounted for by the endoscopic mass screening for the population at risk. Over the decade 1981/90 in our Department 15 EGC were found of a total of 54 operated gastric neoplasms (28 per cent): nine men and six women of mean age of 62 (range 54–84) years, all of them endoscopically diagnosed In 10 cases (66 per cent) the lesion was in the antrum, and five (34 per cent) in body or fundus, the infiltration was limited to the mucosa in six cases (40 per cent), whereas it extended into the submucosa in nine (60 per cent), two histologically type I (13 per cent), three to type II (20 per cent), and 10 to type III (67 per cent) The antral cases (10) were subjected to 4/5 gastric resection with reconstruction according to Billroth II, the remaining five cases were treated by total gastrectomy with Roux-en-Y oesophago-jejunal reconstruction. In all cases a level 3 lymphadenectomy was performed. In two cases (both of them with submucosa extension) nine lymph nodes showed first-level neoplastic positivity. The grading proved G1 in two (13 per cent), G2 in two (13 per cent), and G3 in 11 (74 per cent)

No intraoperative deaths occurred, morbidity showed two subphrenic abscesses evacuated by ultrasound guided drainage, one duodenal stump dehiscence treated with permanent nasogastric tube and total parenteral nutrition, and one lung atelectasis

Follow-up (three annual assessments by gastroscopy, liver ultrasound, chest X-ray, and CEA) shows an 87 per cent overall survival after 5 years (one death due to natural causes and one after relapse at 2 years). Our experience demonstrates an increased rate of detection with careful endoscopic screening of the population at risk

Enteral versus parenteral feeding in gastric cancer patients undergoing gastrectomy: preliminary results

J. Cabrol, L.L. Catot, V. Moral, R. Trallero, M.J. Amengual,
A. Malet, N. Garcia and O. Colomer *Department of Surgery, Hospital de Sabadell, Parc Tauli s/n, 08208 Sabadell, Barcelona, Spain*

Aim: To investigate the effect of early postoperative total enteral nutrition (TEN) *vs* total parenteral nutrition (TPN) on the postoperative outcome in gastric cancer patients undergoing gastrectomy
Patients and methods: Fifty-seven patients who were to undergo curative operations for gastric cancer were randomly allocated to two groups according to the type of postoperative nutritional support Group 1 (n = 27 patients), received TEN through enteral jejunostomy; Group 2 (n = 30 patients) initiated TPN via central venous catheter. In both groups the nutritional support started 24 h following surgical operation Biochemistry panel, nutritional and immunological status, and clinical outcome were assessed prior, 24 h after, and 8 days after surgery. Immunological assessment consisted of quantification of cellular and humoral parameters. Statistical analysis was carried out by analysis of variance (ANOVA).
Results: Eight days after surgery albumin remained steady in TEN and TPN groups when comparing their values with those found 24 h after surgery The rest of the investigations, especially prealbumin, transferrin, total lymphocytes and lymphocytes subsets increased in value, but there were no statistical differences in both groups, except for lymphocytes B and CD4, which recovered more in the TEN group ($P < 0{\cdot}05$). Septic morbidity and hospital stay was greater in the TPN group. The mortality rate was similar in both groups.
Conclusion: TEN seems just as effective as TPN in fed gastrectomized gastric cancer patients, furthermore increases in B and CD4 lymphocytes subsets, has less septic morbidity and is nearly 10 times cheaper

Is artificial perioperative nutrition useful in gastric cancer patients? Nutritional study before and after surgery

J. Cabrol, L.L. Catot, R. Trallero, V. Del Moral,
M.J. Amengual, N. Garcia and O. Colomer *Consorci Hospitalari Parc Taulí, Parc Taulí s/n 08208-Sabadell, Spain*

Aim: To assess the usefulness of perioperative artificial nutrition in gastric cancer patients undergoing gastrectomy
Patients and methods: Two groups of patients were studied. The first one was composed of 72 patients with gastric cancer (GC). The second group was comprised of 57 healthy persons (HP). The sex and age were similar in both groups. In the GC group, biochemistry panel, nutritional and immunological status were assessed prior to and 24 h after surgery. In the HP group, the same kind of investigations were made just 24 h prior to surgery. Nutritional assessment consisted of determination of anthropometric measures. Immunological assessment consisted of determination of cellular and humoral parameters. Statistical analysis was carried out by Student's t-test and analysis of variance (ANOVA).
Results: The values found 24 h prior to surgery in the GC group related to weight, corporal mass ratio, triceps skinfold, haemoglobin, albumin and prealbumin were worse than those found in the HP group ($P < 0{\cdot}05$). Nevertheless the malnutrition that affected the patients of the GC group was considered as mild We found no significant differences in the rest of the parameters studied between both groups. The nutritional status of the GC group patients had no relationship with the stage and the location of the tumour. Twenty-four hours after surgical operation, the biochemical and immunological parameters of the GC group showed a significant decrease compared with the results found in the same group before surgery ($P < 0{\cdot}001$).
Conclusions: (a) Because of the mild malnutrition in GC group patients prior to surgery, the use of preoperative artificial nutrition should be limited to patients who are severely malnourished. (b) The significant decrease of the biochemical and immunological values in the GC group 24 h after the surgical operation, suggests that postoperative artificial nutrition could be useful in this kind of patient.

Gastric cancer: descriptive study and prognosis in our department

J.J. Sánchez Cano, A. Sánchez Marín, J.J. Sánchez Pérez,
J.B. Comes, R. Sala, J. Domenech and
D. Del Castillo Déjardin *Department of Surgery, Hospital Universitari de Sant Joan de Reus, and Universitat Rovira i Virgili, Spain*

Introduction: In Spain, the gastric cancer is believed to be the second cause of cancer mortality in men and the third in women.[1] We present our experience in the diagnosis, treatment and follow-up of this disease.

Patients and methods: Between January 1981 and April 1993 116 patients attended with gastric adenocarcinoma, 39 women (33·6 per cent) and 77 men (66·4 per cent). The average age was 66·18 years (± 14 76 years). We analysed clinical, laboratory, operative and postoperative data The 5-year survival has been calculated using the Kaplan and Meier method [2]
Results: All the patients were symptomatic. The first diagnostic tool was gastroscopy (60 3 per cent, 70 patients), upper intestinal X-rays (32·8 per cent, 38 patients) and laparotomy (6·9 per cent, 8 patients) Fourteen patients (12·1 per cent) had family history of gastric cancer and 21 patients (18·1 per cent) had risk factors for this disease The antrum was the most frequent site (49·1 per cent, 57 patients) Bormann III was the most frequent macroscopic type (64 7 per cent, 75 patients). Of 116 patients attended, 14 patients (12 1 per cent) were not eligible for surgery; of the remaining patients (87·9 per cent, 102 patients), 61 patients (52·6 per cent) were resected. D1 lymphadenectomy was performed in all the resections. The global postoperative morbidity was 39·2 per cent (40 patients) and postoperative mortality was 16·6 per cent (17 patients) In patients with resection morbidity was 45·9 per cent (28 patients) and mortality 16·3 per cent (10 patients). Patients with resection that died had an advanced stage (three patients had E IIIa and seven patients had E IV). Mean postoperative stay was 18·7 days (± 13 57). The staging was: E Ia 6 patients (5·2 per cent), E Ib 10 patients (8·6 per cent), E II 8 patients (6·9 per cent), E IIIa 18 patients (15·5 per cent), E IIIb 3 patients (2·6 per cent) and E IV 65 patients (56 per cent). Overall 5-year survival was 13 per cent: 5-year survival based on staging was: E Ia 100 per cent, E Ib 50 per cent, E II 0 per cent, E IIIa 9 per cent, E IIIb 0 per cent and E IV 0 per cent.
Conclusions: The morbi-mortality is influenced by the high percentage of patients with stage IV The low survival of the stages II and IIIa can be attributed to staging problems given that we did not perform D2 lymphadenectomy. Since April 1993 we applied the Japanese diagnosis and treatment protocol of gastric cancer[3] and we await our future results

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Acknowledgement to A Fallada Pouget for the translation.

The importance of peritoneal washing CEA measurement in gastric cancer

B. Çetin, C. Koksoy, S. Kutun, H. Ulucanlar, M Aldan and A. Çetin *Department of Surgery, Ankara Oncology Hospital, Ankara, Turkey*

The aim of this study was to find out whether the measurement of carcinoembryonic antigen (CEA) in peritonal washing is superior to serum in gastric cancer

At the time of laprotomy peritoneal washings and blood samples were obtained from 41 patients with gastric cancer invading the serosal layer of stomach and 16 patients undergoing laparotomy for benign reasons. The gastric cancer group consisted of patients with hepatic metastases ($n = 19$) and patients with peritoneal dissemination ($n = 10$). The CEA levels in the collected samples were measured by radioimmunoassay and cut-off level was set at 5 mg/ml in this study.

Although the patients with hepatic metastases had elevated CEA levels, there was no difference between the results of two sample collection methods Peritoneal washing CEA levels were higher in the patients with peritoneal dissemination ($P < 0\ 05$) Moreover the patients with both hepatic metastases and peritoneal dissemination had higher peritoneal CEA levels than the patients with either hepatic metastases or peritoneal dissemination and benign disorders ($P < 0{\cdot}05$)

Both peritoneal washing and serum CEA measurements are high in the presence of hepatic metastases. But the peritoneal washing CEA measurement is only valuable to detect peritoneal dissemination

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Surgery in the staging and long-term survival of patients with gastric B-cell MALT lymphoma

P. Chirletti, R. Caronna, M. Martelli, P. Piovanello, D. Calcaterra and V. Stipa *Patologia Chirurgica IX, Cattedra di Ematologia I, Universita di Roma 'La Sapienza', 00161 Rome, Italy*

Aim: To assess the value of surgery in the treatment of gastric B-cell MALT lymphoma.
Introduction: Gastric B-cell MALT lymphomas (5 per cent of all malignant gastric tumours and approximately 70 per cent of primary gastrointestinal lymphomas) respond better than gastric carcinomas to chemotherapy The chief prognostic indicators are histopathological grading (according to Working Formulation: low-grade or high-grade) and disease stage (according to the Mushoff classification). The role of the surgery in the treatment of gastric B-cell MALT lymphoma remains controversial. Recent studies report no difference in the long-term survival of patients with early stage disease treated by chemotherapy with or without surgery Because outcome depends on correct staging, the question is: can patients be accurately staged without laparotomy? Our study had two aims· to verify whether surgery helps in staging of gastric B-cell MALT lymphoma and whether it is helpful even in advanced stage disease.
Patients and methods: From 1987 to 1995, 17 consecutive patients (10 men, seven women; mean age 58 years) were admitted for treatment of gastric B-cell MALT lymphoma. Preoperative staging (oesophagogastroduodenoscopy, total-body CT-scan and bone marrow biopsies) classifed 14 patients as Stage IE, two as Stage IIE, and one as stage IVE (according to the Ann Arbor Classification) During laparotomy four patients had total gastrectomy for proximal or diffuse neoplasms and 13 had partial gastrectomy for neoplasms in distal sites. Intraoperative staging comprised bilateral liver biopsies and exploration of all abdominal lymph nodes with biopsies of suspicious nodes). All patients received postoperative chemotherapy, according to the protocols used by the Department of Haematology.
Results: None of the 17 patients died and none had major complications related to surgical treatment. Staging laparotomy showed that four of the 17 patients (23·5 per cent) had been understaged (IE instead of IIE). Histological classification according to the Working Formulation disclosed 6 low-grade and 11 high-grade malignant lymphomas All patients responded to chemotherapy. Kaplan–Meier curves yielded a 5-year survival rate of 90 per cent (9/10 patients) in Stage IE, 83 per cent (4/6 patients) in stage IIE Total and partial gastrectomy resulted in similar outcome.
Conclusions: Surgery has a significant role in the treatment of gastric B-cell MALT lymphoma It will often (23 5 per cent of our cases) correct clinical understaging without morbidity and mortality and help to guide chemotherapy. Five-year survival in our series (90 per cent) is the same as that referred to by others. We observed a long-term survival also after 60 months. In advanced disease (Stage IVE) surgery has a useful debulking effect (one of our patients with Stage IVE disease is still alive 84 months after the operation)

Surgery for gastric cancer in the elderly: our experience

L. Corbellini*, R Vellucci†, L. Toppi† and F.M. Di Matteo†
**General Surgery, University 'G. D'Annunzio', Chieti, †IIIrd Surgical Clinic, University of Rome 'La Sapienza', Italy*

A significant increase in gastric cancer, especially in the elderly, and its severe prognosis needs an aggressive surgical philosophy The aim of this study is to evaluate surgery for this elderly group in relation to age, cancer location, staging and survival

From January 1985 to December 1994, 163 patients were operated on for gastric cancer Forty-nine were over 65 years old (range 65–89 years), 33 males and 16 females (M/F 2·06:1). Fifteen patients were classified as stage I, 13 as stage II, 20 as stage III and one as stage IV. Follow-up has been made up to March 1996 (range 180–24 months). The site of gastric cancer related to stage has been antrum in 11, and body in four at stage I, antrum in nine, body in three and one in fundus on stage II, antrum in 12 and body in seven on stage III and finally in fundus in only one at stage IV. On 25 patients we performed Total Gastrectomy (TG), R3 lymphadenectomy and oesophago-jejunum anastomosis Roux-en-Y, and on 23 patients Gastric Distal Resection (GR), R2 lymphadenectomy, with a Billroth II mechanical anastomosis One patient was subjected to palliation. Eight TG and seven GR on stage I were carried out, seven TG and seven GR at stage II, 10 TG and nine GR at stage III and one palliation at stage IV.

Results: These, related to type of operation and stage, show that 19 out of all 49 patients operated on are still alive (38 7 per cent). Of them five who underwent TG and four GR at stage I, three to TG and two GR at stage II and two TG and three GR on stage III [10/25 TG (40 per cent) and 9/23 GR (39·1 per cent) are still alive]. If selection is carried out among the patients who were 65–75 years old (Group A) and between those over 75 (Group B) in order to emphasize some possible differences related to survival, we can see that still 17/37 patients (45·9 per cent) in the first group and two out of 12 patients in the second group are alive (16·6 per cent, in this group we performed one TG, and one GR). In the Group A patients we also performed TG and GR at stage I, II and III. For the fundus gastric cancer we performed TG 'de necessite' In Group B patients, in the antrum gastric cancer, we peformed only GR, in the body and fundus cancer we performed TG. In the Group A patients (65–75 years) in the antrum cancers, TG and GR obtain the same survival rate However, if we consider also the body cancers, TG achieves a better survival. The global survival (including also the body cancers) is better after TG. Cancers of the fundus have the most severe prognosis. In the Group B patients (over 75 years) survival after TG and after GR is identical (1/16). We think that age and general conditions seem to have influenced our operation choice for the antrum cancer. we thus performed only GR. If we relate the stage and location of cancer with the type of operation, TG seems to get a better global survival rate in the Group A patients than in that of the Group B Morbidity and operatory mortality is the same in both groups. We think that in elderly patients gastric cancer surgery has been aggressive, but in relation to age and general conditions If these allow we prefer to perform TG in antrum cancers as well.

Surgery of morbid obesity: results of annular vertical gastroplasty

M.J. García-Coret, A. Vásquez, R. Villalba, D. Dávila, E. Montalvá, E. Pareja, C. Fuster, J. Asensi, F. Peiró and R. Trullenque *Service of General Surgery and Research Centre, Valencia University General Hospital, Valencia, Spain*

Pathological obesity reduces life expectancy and is associated to numerous disorders. The costs are important: in the USA, 57 per cent of the total healthcare expenditures in type II diabetes have been attributed to obesity. The fundamental aim of treatment in these cases is to reduce body weight (on average, by 5–10 per cent) and maintain it at levels that diminish health risk. We report our experience in the management of morbid obesity by annular vertical gastroplasty. A total of 28 patients were operated on for medication-refractory pathological obesity over a 9-year period (January 1987 to May 1995) The study was divided into two periods (1987–1989 and 1990–1995), as during the first period annular vertical gastroplasty was performed using the round ligament, while in the later period an annullated marlex mesh was employed An evaluation was made of the complications of surgery and of the results obtained in terms of weight loss and its maintenance The first period comprised 10 patients, *vs* 18 in the second Mean patient age was 40·2 years (range 19–56 years), with a clear female predominance (85·71 per cent). In six cases there were family antecedents of obesity, and 12 patients suffered from some form of psychiatric disorder (mainly depression). Body weight ranged between 95 and 200 kg (mean 148 kg), with a height of 149–183 cm (mean 148 cm). Surgery was performed after failure of medical treatment (monitored by the endocrinologist). Repeat surgery was required in three cases belonging to the first period, replace the round ligament with a marlex annulus. A total of 13 cholecystectomies were associated to the management of obesity, due to the presence of gallstones There were no surgical complications of note Surgical wound infection was observed in six cases. In the immediate postoperative period vomiting was the most common manifestation (four patients) There was one case of partial gastroplasty dehiscence. Mean hospital stay was 12 7 days. There were two deaths Subsequent morbidity most often involved vomiting (13 cases) and pyrosis (five cases). Two patients failed to lose weight, one suffered repermeabilization of the gastroplasty, and two developed stenosis. Three cases of peptic ulcer were recorded (one with upper gastrointestinal bleeding), and one patient suffered from diarrhoea that responded to medication. During follow-up (mean duration 21·4 months, range 12–100 months), the mean final body weight was 98 kg (range 87–137 kg) In conclusion, dietary restriction and an increased energy expenditure is central to the management of obesity Although this seems a simple solution, it is extremely difficult to achieve in practice Surgery is therefore a practical alternative in those cases in which medical treatment fails In this sense, annular vertical gastroplasty affords a good decrease in body weight, despite the morbidity–mortality involved.

Problems of surgical technique and tactics in complicated postbulbar ulcers

A. Cotîrleţ, I. Ivan, D. Ghiuş and M. Cotîrleţ *Surgical Clinic, Hospital Moineşti, Romania*

The authors report on their experience from 80 patients with complicated postbulbar ulcers (9 per cent of duodenal ulcers) with haemorrhage (20 cases) perforation (six cases), duodenal stenosis (18 cases) and penetration pancreatic-hepato-biliary (36 cases) during 1987–1995. The frequency of haemorrhagic complication was of 25 per cent. As the haemorrhage due to postbulbar ulcer is more likely to be due to vascular involvement, the severe character of the haemorrhage and the frequency of recurrence, mainly cataclysmic, requires radical surgery as early as possible. The following were used Polya's gastrectomy (10 cases) Péan's gastroduodenectomy + vagotomy (seven cases), gastrectomy for exclusion with haemostasis *in situ* and ligature of gastroduodenal artery + vagotomy (two cases) and pyloroplasty with vagotomy and haemostasis (one case).

In 16 cases with perforation. Reichel-Polya's gastrectomy in two patients, Péan's gastrectomy in two cases, excision pyloroplasty and suture of the perforation in one case, were used, respectively.

In the postbulbar ulcers penetrating into the pancreas or into the hepatic pedicle the following were performed: Reichel-Polya's gastrectomy (six cases), Péan's gastrectomy (14 cases of which 12 were with vagotomy) gastrectomy for exclusion of ulcer in 16 cases of which 14 were with vagotomy In 14 patients with stenosed ulcers, Reichel-Polya's gastric resection (four cases), Péan's gastrectomy (eight cases), gastrectomy for exclusion (six cases) were used.

The conclusions may be drawn that the postbulbar ulcers are complicated ulcers that require different surgical treatment, as early as possible. in order to reduce postsurgical morbidity and mortality (7·5 per cent mortality).

Gastric cancer: staging and curability

A. Fosson, F. Sansonna, M. Pennisi, U. Parini and P Dessanti *Surgery Department, Regional Hospital of Aosta, viale Ginevra 3, 11100 Aosta, Italy*

From 1980 to 1995 in the Aosta Regional Hospital 345 patients affected by gastric neoplasm were operated on. There were 328 adenocarcinoma, 10 lymphomas, one undifferentiated carcinoid, one adenoma with severe dysplasia, two leiomyosarcomas, one leiomyoblastoma and two leiomyomas In 5 cases (1·5 per cent) the onset of malignancy occurred after subtotal gastrectomy for benign disease. Allegedly, the incidence of gastric cancer has been decreasing compared to a few decades ago, but in spite of this data, and allowing for a small number of cases, no change in prevalence and incidence over the last two decades was found in our region. The mean age was 67 years (range 42–86 years) and males were more affected (64 per cent) than females (36 per cent) by adenocarcinoma of the stomach. Adenocarcinomas were divided as per Lauren classification into intestinal adenocarcinoma, diffuse infiltrating carcinoma and mixed type; 20 were early cancers (6 per cent), and the most common tumour sites were the antrum and distal stomach (49 per cent). Currently in addition to the usual pre-operative examinations, both laparoscopy to avoid unnecessary laparotomies in case of advanced unresectable cancer, and the sensitivity of marker CA 72/4 are being examined After the first period (1980–1989) mandatory total gastrectomy was given up, and total gastrectomy is now performed only when necessary, i.e when distal resection is not feasible either because of tumour site (proximal tumours) or because of the extension of the tumour, on intraoperative gastric biopsy For Lauren diffuse carcinoma the resection is carried out at 8–10cm from the tumour site, and at 3–5cm in case of intestinal adenocarcinoma. One hundred and thirty-three total gastrectomies, 13 total degastrectomies, 138 subtotal gastrectomies and two polar resections for proximal tumours were done. the Roux-en-Y reconstruction was preferred Generally a D2 lymphadenectomy was carried out, but D3 lymphadenectomy was chosen in case of advanced cancer, together with resection extended to colon, pancreas and liver. In two cases a pancreas-preserving operation in case of middle stomach neoplasm infiltrating the body of the pancreas was performed, without serious morbidity Operative mortality was 3·5 per cent and actuarial survival at 5 years (operative mortality excluded) was 31 per cent depending more on nodal status rather than on tumour level. For the last 3 years a post-operative adjuvant chemotherapy followed surgery; it was well tolerated but conclusive data are not yet available.

Does lymph-node dissection for gastric cancer surgery have a therapeutic value?

A. Gutiérrez, E. Tobaruela, A. López, I. Lasa, P. Hernández, M. Diez, A. Duce, J.M. Muguerza, J.M. Enríquez, F. Hernández and J. Granell *Hospital Universitario Príncipe de Asturias, Servicio de Cirugía General, Ctra. Alcalá-Meco s/n, 28805-Alcalá de Henares, Madrid, Spain*

Introduction: Although for Japanese authors, lymph-node dissection has a definite therapeutic value, it was not until 1994 that it appeared in western publications to show an improved survival with extensive dissections *vs* standard. Nevertheless this is still a matter of controversy. The aim of this study is to evaluate in our patients, studied according to the criteria of the Japanese Society for the Research in Gastric Cancer (JSRGC), as to whether an extended lymph-node dissection (D2/D3) is associated with an improved survival, or only contributes to improved staging and a definite prognosis more precisely.
Patients and methods: From March 1988 to March 1996, 157 patients have been operated on for gastric adenocarcinoma in our Department Clinicopathological variables as well as the definitions of surgery were evaluated according to the criteria of the JSRGC.
Results: The resection rate in our series is 84 per cent, with 78 per cent presenting with advanced disease (stages III–IV). Sixty-three total and 68 subtotal gastrectomies were performed Lymph-node dissection was: D0 in three; D1 in 54; D2 in 65, and D3 in nine patients, respectively. Postoperative lymph node involvement for resected tumours was. N1 37, N2 27, N3 13 patients Surgery was defined as absolutely curative in 64 (41 per cent), relatively curative in 23 (15 per cent) and not curative in 70 (44 per cent). Postoperative morbidity and mortality were 22 per cent and 4 per cent for D1, and 18 per cent and 9 per cent for D2–D3 dissections For patients without lymph-node involvement, overall probability of survival with D1 dissection was 67 per cent *vs* 54 per cent for D2–D3 (not significant) For patients with N1 lymph-node involvement, survival with D1 was 0 per cent, and 58 per cent for D2–D3. With N2 involvement and D2–D3, overall survival was 20 per cent.
Conclusions: A wider lymph-node clearance is not associated with a significantly higher postoperative morbimortality, and, when there is no lymph-node involvement, a more extensive lymph-node dissection adds nothing in terms of survival, but when there is lymph-node involvement, patient survival improves with a more extensive dissection

Extramucosal pyloromyotomy as a procedure of gastric drainage after truncal vagotomy: experimental study in rats

M. Hernández, C. Pérez, J Sánchez, A. Blasco, M. Martín, D. Llop and D. Del Castillo *Unit of Experimental Surgical Research, Hospital Sant Joan and School of Medicine and Health Sciences, Rovira i Virgili University, Reus, Spain*

Truncal vagotomy (TV) reduces the ability of the stomach to empty and necessitates a drainage procedure such as pyloroplasty The use of other types of vagotomy to avoid gastric paresis introduces technical difficulties and leads to an increased incidence of ulcer recurrence The purpose of this study is to assess the effectiveness of extramucosal pyloromyotomy to improve gastric drainage after TV.
Materials and methods: Thirty Sprague–Dawley rats weighing 200g were divided into three groups Group 1: TV alone, Group 2 TV + pyloroplasty; Group 3. TV + pyloromyotomy. To assess gastric emptying, the size of the different parts of stomach (greater curvature (mm), lesser curvature (mm), pylorus (mm) and gastric anterior surface (mm^2) were measured at the time of surgery and after 10 and 30 days These measurements were carried out by an image processing and analysis system (Quantimet 500c, Leica).
Results: The size of greater and lesser curvatures, and gastric surface was not shown to be significantly different between Groups 2 and 3. The Group with TV alone (Group 1) showed a significant increase in values for greater curvature and gastric surface due to gastric retention
Conclusion: Extramucosal pyloromyotomy appears to have a similar effect upon gastric emptying as pyloroplasty and could reduce complications related to formal pyloroplasty

Gastric stump carinoma: management of advanced cancer

J. Kocik, T. Berns, H. Nottberg and B. Reers *Chirurgische Universitätsklinik Münster, Waldeyerstraße 1, 48129 Münster, Germany*

The results of a retrospective analysis of cases of carcinomas of the gastric stump are presented.

Between January 1984 and December 1994 a total number of 61 patients were operated on Mean age of the patients was 62·9 years, the male:female ratio was 6 1 In 59 out of 61 patients the original operation performed was a Billroth II resection. Thirty-nine patients underwent total gastrectomy with or without D2 lymphadenectomy The resectability rate was 75 per cent (46 patients). Adjuvant chemotherapy (mostly FLE patterns) was administered to eight patients Thirty-four out of 61 cases were classified as far advanced (stage III and IV, according to the UICC classification), early cancer was found in 20 cases. The 5-year survival rate was 21 per cent for all patients In the case of advanced cancer prognosis was extremely bad. Only one out of 35 patients survived 5 years. Median survival was 22·9 months ($n = 1$) and 9 2 months ($n = 2$), respectively. There was no better survival in those patients who received adjuvant chemotherapy (median survival 14 2 months).

We conclude that beside systematic endoscopic examination 10 years after surgery for benign gastric diseases a radical approach in operation technique including D2 lymphadenectomy or multivisceral resection is essential for a better prognosis of advanced cancer of the gastric stump

Evaluation of duodenogastric reflux and antral motility by colour Doppler sonography in patients undergoing cholecystectomy

J.R. Ladny, J. Polakow, J. Laszkiewicz and Z. Puchalski *Departments of General Surgery and Radiology, Medical University of Bialystok, ul. M Sklodowskiej-Curie 24a, 15-276 Bialystok, Poland*

Background: Duodenogastric reflux (DGR) is a common gastroduodenal motility disorder which may lead to inflammatory alteration of gastric mucosa and peptic ulcers Various diagnostic methods for DGR have been used to date Because these methods are invasive, the authors tried to evaluate duodenogastric reflux, along with antral motility and gastric emptying of a liquid meal by colour Doppler sonography.

Material and methods: Fifty-three patients (15 males and 38 females) aged 35–56 years, having previously undergone open or laparoscopic cholecystectomy, underwent colour Doppler sonography (CDS) according to Fuimura *et al.* Duodenogastric reflux, antral motility, and gastric emptying of 400 ml liquid meal were evaluated. A Toshiba SSA-140A unit with Convex probe 3·75 mHz was used. Twenty-three asymptomatic healthy volunteers served as a control group.

Results: This approach was feasible in 51 (96·2 per cent) of the 53 subjects studied. Duodenogastric reflux was demonstrated in 16 (59·3 per cent) of the 27 patients who underwent open cholecystectomy and 22 (84·6 per cent) of the 26 patients after laparoscopic procedure and only in three (13 per cent) of the healthy volunteers. The frequency of the duodenogastric reflux were significantly increased in patients with laparoscopic cholecystectomy as compared with open cholecystectomy and asymptomatic volunteer groups. Gastric emptying and motility index of antral contractions were significantly decreased in these patients.

Conclusion: Colour Doppler sonography is useful for evaluating of gastroduodenal motility, especially in patients undergoing laparoscopic cholecystectomy. This simple, non-invasive method can be used to understand the pathogenesis of such disorders.

The use of truncal vagotomy and pyloroplasty for duodenal ulcer complications

P Laizans*, I. Vegnere*, A. Zolovkins*, A. Lombardi†, A. Sirgeda* and M. Mihelsons **Department of Surgery, Riga 7th Hospital, Medical Academy, Latvia, and †1st Department of Surgery, University 'La Sapienza' Rome, Italy*

For the treatment of duodenal ulcer (DU) complications there is again the controversy over merits of the best method of choice. We report our experience about the treatment of this pathology by bilateral truncal vagotomy (TV) with pyloroplasty

Between 1986 and 1993 we operated on 130 patients (95 males and 35 females, mean age 51 4 years, range 19–81 years) with DU showing the following complications· duodenal bleeding in 64 patients (49·2 per cent), perforation in 40 patients (30·8 per cent) and stenosis in 26 patients (20 per cent) Forty-one patients (31·5 per cent) had had no previous medical history of DU In case of duodenal bleeding we chose to perform ulcer stitching followed by pyloroplasty according to the technique described by Heineke-Mikulicz (H-M). When an ulcer was located on the anterior duodenal wall, patients underwent Judd operation H-M procedure was used in all cases of stenosis and Judd technique in presence of perforation. Mortality occurred in four patients (3·1 per cent). Postoperative complications developed in 12 patients (9·2 per cent). two patients were reoperated on for the occurrence of small bowel obstruction; wound infection was present in two; diarrhoea in seven and transitory dysphagia in one patient.

One hundred and five patients (83·8 per cent) were followed up for a mean time of 6·5 years (range 3–10 years). Two patients died from causes unrelated to treatment Four patients (3·8 per cent) have had recurrent DU, two (1·9 per cent) showed symptoms of mild Dumping syndrome; mild stomach motility impairment was present in two (1·9 per cent); three (2·9 per cent) sometimes suffered from epigastric pain in which endoscopy showed duodeno-gastric reflux According to the VISICK classification the results of the operation were as follows. Group I – 84 patients (81·6 per cent); Group II – 11 patients (10·7 per cent), Group III – four patients (3 9 per cent); Group IV – four patients (3 9 per cent)

TV with pyloroplasty is an effective treatment of complicated DU and guarantees results similar to the other known types of operation used for this pathology.

A rare Mallory–Weiss lesion: stomach rupture

G. Lauzikas and R. Lunevicius *General Surgery Clinic, 2043 Vilnius University Emergency Hospital, Lithuania*

We describe a rare variant of the Mallory–Weiss syndrome Some elements are typical for this case. the mechanical origin of injury of the gastric wall during vomiting after an excessive consumption of alcohol, with haemorrhage into the stomach

Case report: A 54-year-old man felt an acute pain in the epigastric region during vomiting. Diffuse peritonitis and perforated peptic ulcer was suspected on admission, because pneumoperitoneum was seen in the X-rays. An upper middline laparotomy was performed Three litres of serofibrinous liquid was found in the peritoneal cavity. The maximal concentration was found at the lesser omentum. No gastric or duodenal perforation was found, but after division of the lesser omentum, an 8-cm linear gastric lesser curve rupture was detected· the proximal rupture point was situated in the cardia 1 cm from the oesophagogastric junction, with the defect stretching to the middle of the lesser curve. A small amount of fresh blood and clots were found in the gastric cavity. Visually and to palpation the ruptured stomach sides were soft, without pathological change. Histological analysis showed normal gastric tissue No other pathology was observed in the stomach cavity. The stomach was sutured with vicryl in two layers.

Conclusions: This case report demonstrates the following rare elements of the Mallory–Weiss syndrome. (a) the size of the gastric injury a transmural rupture of almost half of a stomach, (b) the site of the transmural rupture. the lesser curve of the stomach between the two layers of the lesser omentum.

The use of staplers in gastric resection

G. Lippolis, P. Calò, M. Monti, A. Brescia, K.P. Zeri, F.M. Di Matteo, G. Bianchini, F. Boccaccini and G. Palazzini *III Department of Surgery, University 'La Sapienza', Rome, Italy*

The authors report on their experience regarding the use of staplers in the reconstruction of the digestive tract continuity after gastric resection They described the correct execution, the necessary technical precautions, the type of instruments they use in gastric resection and reconstruction for Billroth I, Billroth II, proximal gastric resection and Roux-en-Y reconstruction

Their technique is different from the typical gastric reconstruction for Billroth II proposed by Ravitch and Steichen[1] or Dickman as the authors usually make the gastro-intestinal anastomosis before specimen excision and stapling of the gastric remnant.

Of 161 gastric resections and reconstructions with stapling devices, the authors report seven complications· three (1·8 per cent) anastomotic stenoses, two in Billroth I reconstruction and one in Billroth II; four (2·4 per cent) anastomotic haemorrhages, one in Billroth I reconstruction and three in Billroth II, no anastomotic dehiscence or leaks occurred. Stapling devices allow excellent anastomosis with reduced trauma to the anastomotic lines especially where resected by the surgical circular blade at the same time as the closure of the staples Moreover the closure of the staples in B form allows intramural vessels to reach the resection margin.

In conclusion the use of stapling devices, thanks to their easy use. simplifies the execution and reduces the operating time for gastric resections providing excellent results

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Systematic extended lymph node dissection in gastric cancer

G De Luca, R. Brancher, V. Barbaliscia, M. Mariani, C. Di Francia, C. Guglielmi and G.C. Baita *Department of Surgery, 'E. De Sanctis' General Hospital, Genzano di Roma, Italy*

Japanese experience has shown that an aggressive treatment of gastric cancer with an extended lymph node (N) dissection improves long-term results in survival rate of 10–20 per cent for all stages of disease compared to the results obtained by western authors.[1] Radical resection (D) in Japan is D2 (N1 and N2 dissection) or D3 in advanced cases (D1, D2 and D3 dissection) whereas only in 27 per cent of European Centres is this performed.[2] In a series of 104 consecutive cases of gastric cancer, subtotal or total gastrectomy with extended lymph node dissection (D2–D3) was performed following the Japanese approach in order to reproduce their results. Eighty-nine of 104 patients underwent a resection (85·5 per cent compared with 94·2 per cent in Japan): 22 were early gastric cancer, 67 advanced gastric carcinoma. Fifteen patients were inoperable. Five-year survival rate of all 104 cases 60 per cent (67·5 per cent in Japan)[2]; in resected patients it was 100 per cent in stage I; 77 per cent in stage II; 47 per cent in stage IIIa; 18 per cent in stage IIIb, 0 per cent in stage IV.

The effectiveness of extended lymph node dissection for treatment of gastric cancer is a long-standing problem. In our series, radical resection did not improve the postoperative mortality rate and results showed that 5-year survival rate is similar to Japanese experience for stage I, II and IIIa. Probably oncologic multimodal treatments are required to improve results in other stages. In Europe, similar results have been recently reported from other authors. Although a randomized prospective study has still to be performed, our results support the Japanese approach to gastric cancer.

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Microinvasive carcinoma in multiple hyperplastic gastric polyps

E. Martinez-Mas, V. Pareja, F. Caro, J. Ramos and
J. Segui *Hospital Francesc de Borja, Gandia, Valencia, Spain*

Indications for the excision of hyperplastic polyps are not generally agreed. The incidence of malignant changes found in these polyps is reported to be between 0 and 6 per cent. In contrast, adenomatous polyps are recognized to have malignant potential, and current practice dictates endoscopic or surgical excision, particularly when the size of these polyps exceeds 2cm. We report on a case in which multiple hyperplastic gastric polyps, from fundus to antrum, required total gastrectomy. Microinvasive and multifocal carcinoma was seen in two of these polyps.

Case report: A 61-year-old man was found to have multiple gastric polyps at the endoscopy for the investigation of haematemesis. Biopsies and macrobiopsies of this lesion showed hyperplastic gastric mucosa (Nakamura I). Because of the number (more than 50), size (between 0·5 and 3cm) and shape (sessile) of the polyps, total gastrectomy was performed. No morbidity or recurrence has been identified in 2 years of follow-up. The excised specimen contained multifocal microinvasive carcinoma in two of the largest polyps, lymph nodes were disease-free.

Discussion: This case supports the contention that hyperplastic polyps in the stomach may progress through stages of activity as increasing neoplastic potential as size increases. Without complete excision (even total gastrectomy) and scrupulous microscopic study, the possibility of carcinomas arising in hyperplastic polyps cannot be completely excluded.

Locally advanced gastric carcinoma: role and results of extended resection

A. Mattana, O. Nardello, A. Cois, C. Gromo, A. Pisanu and
A. Uccheddu *Istituto di Chirurgia, Università di Cagliari, Ospedale S. Giovanni di Dio, via Ospedale 46, 09124 Cagliari, Italy*

Advanced carcinoma of the stomach often invades neighbouring organs requiring an aggressive surgical approach for removal from adherent structures. Morbidity and mortality rates for extended gastric resection, is higher than non-extended resections, and requires careful patient selection and a clear demonstration of a long-term beneficial effect from the procedure. The aim of this study is to examine early and late results of extended gastrectomy with multiorgan resection in an effort to determine whether this operation is worthwhile.

Between 1970 and 1995 an extended gastric resection for locally advanced gastric carcinoma was performed in 57 patients. No distant metastasis was evident in 52 (91·2 per cent); liver or omentum metastases were present in five (8·8 per cent). A total gastrectomy was performed in 34 (59·6 per cent), a subtotal gastrectomy in 23 (40·4 per cent). A complete lymph node dissection was associated with 'en-bloc' resection of spleen (28), thoracic oesophagus (14), transverse colon (17), pancreas (19), liver (6), diaphragm (3), gallbladder (2), adrenal gland (1), abdominal wall (1). A carcinomatous infiltration was histologically demonstrated in 36 (63·2 per cent), a pseudotumourous inflammatory adhesion in 21 (36·8 per cent). The overall postoperative morbidity rate was 52·6 per cent: 58·8 per cent after extended total gastrectomy (ETG) and 43·4 per cent after extended subtotal gastrectomy (ESG). Postoperative mortality rate (30 days) was 22·7 per cent: 26·4 per cent after ETG and 17·2 per cent after ESG. A relationship between mortality and the organ resected was evident for extension to the pancreas (six out of 13 deaths). The 3- and 5-year overall survival rates (Kaplan–Meier) were 53·3 per cent and 42·5 per cent; 57·6 per cent and 44·7 per cent after ETG and 49·9 per cent and 40·9 per cent after ESG.

The authors conclude that an aggressive surgical approach for locally advanced gastric cancer involves a high postoperative mortality and morbidity, but allows a better quality of life, prevents malignant complications, increases immunology defences and determines a longer survival in comparison with palliative procedures.

The early phases of gastric cancer development and computer simulation: a new approach to the research

F. Meneghini, L. Stellin, R. Biancastelli, M. Anniballi and
E. Leonzio *'G. D'Annunzio' University, Emergency Surgery Centro Se. Bi-Via dei Vestini 31, 66013 Chieti, Italy*

Purpose: The results of surgery in the treatment of gastric cancer are poor and discouraging, mainly in the advanced form. Despite the growing knowledge of its clinical features and lympho-nodal spreading (Maruyama studies), the survival rate has not basically improved in the last 10 years. An important problem to solve in this kind of approach is that up to now the availability of pathological specimens of gastric cancers in their very early phases of growth (micro-carcinoma, 1–3mm wide) is poor, not allowing a detailed study on this subject. To this end, we have thought it possible to reproduce, by a computer simulation, the early phases of cancer growth in a stepped way, by elaborating the scarce information available about the gastric cancer biology and comparing our results with the more abundant data about the well-developed, advanced forms.

Method: A simulating model has been designed on data coming from *in vivo* and *in vitro* sites on tumour pattern growth, clinical data coming from humans affected by neoplastic disease in its first stage, pathological specimens and trying to guess by logic induction the main features of the biological phenomena which affect tumour growth. We considered 12 parameters which are representative of the most important variables affecting tumour growth and their interrelationship with the surrounding tissues. To improve the computing power in the production session the software programs are designed in parallel form to be able to operate in a multi-computer system.

Results: First results show that a 20 per cent lowering of the neoplasic cell migration rate leads to a final number of cells (55,972) that is 270 per cent bigger than the control group, showing a mean of 21,008 cells. This first result is an incentive to investigate, by means of simulations, more deeply into the early phases of tumour development.

Conclusion: In our model, the cell migration rate noticeably affects the tumour growth. The program we are working on is presently in its initial stages but, when accomplished, it could play a substantial role in building a bridge between the laboratory and clinical observations, helping to work out the intertwined relationships between gastric cancer biology, lymphatic spreading and therapeutic results.

Lymphadenectomy in gastric cancer

M Mele, G. Mezzetti, P.L. Bianchi, S. Arcieri, M. Varriale, F.M. Di Matteo, N. Peparini, S. Maggi, A.M. Romani and A Filippini *III Surgical Department, 'La Sapienza', University, Rome, Italy*

Introduction: Different results obtained by Japanese and western surgeons in the treatment of gastric cancer have suggested the establishment of a multicentre prospective study about extended lymphadenectomy in gastric resection for cancer. All patients entering the study group have been pre- and intraoperatively evaluated for the site of neoplasia, the penetration through the gastric wall, the pathological pattern, grading and staging. Node involvement has been classified according to both TNM and JRSGC classification
Methods: From 1971 to May 1996, 310 patients were operated on for gastric cancer. Two hundred and ten underwent total gastrectomy, 70 underwent subtotal gastrectomy and in 30 cases a palliative procedure was performed. Since March 1992, 55 patients who have been operated on with extensive lymphectomies were evaluated prospectively and preliminary analysis of the data are now available
Conclusions: Statistical conclusions cannot be reached yet because of the small number of patients treated However, the authors are able to define some technical guidelines that have an impact on the oncological value of surgery

Bleeding peptic ulcer in Riga City: retrospective study

M. Mihelsons, G. Pupelis and K. Arklins *Latvian Medical Academy, Riga, Latvia*

The hospitalization and surgery for uncomplicated ulcers has decreased in Europe in the last decade, but the number of hospital admissions for haemorrhage associated with ulcers has remained relatively unchanged. Contrary to that, a progressive elevation of the number of bleeding patients during the last 6 years was observed in Riga.
Aim: Our retrospective study was to determine possible reasons that could affect the growing rate and clinical outcome of bleeding patients, and find out ways to ameliorate the situation.
Methods: Retrospective analysis of hospitalization rate, clinical outcome and anamnesis associated with bleeding from peptic ulcer in the Riga city hospitals was done for the time period 1990–1995
Results: Our data provide evidence of growing rate of bleeding associated with peptic ulcer There were totally 184 cases in 1990 and 434 cases in 1995, comprising 5·3 per cent and 7 per cent of all hospitalizations for abdominal emergencies, respectively. The overall mortality reached 9·8 per cent (18) in 1990, but, despite the growing number of bleeding ulcers, mortality has decreased to 6·7 per cent (29) in 1995 Riga's 7th Hospital rate was 356 admissions during the last 3 years (1993–1995), 223 patients were treated surgically (62·6 per cent). Mortality rate for surgery was 7·6 per cent (17) and for non-operated patients 133 (6·7 per cent) The overall mortality was 7·3 per cent, similar rates to those reported by European surgeons.
Conclusions: (a) The bleeding associated with peptic ulcer is mainly caused by uncontrolled use of NSAIDs and alcohol abuse; (b) relatively high mortality during the last years reflects our limited resources for non-surgical treatment and relatively high number of patients in poor condition; (c) high rate of surgical activity and average mortality rate comparable with reports from Europe demonstrates that surgical method is still a good and safe alternative; (d) an improvement of socio-economic conditions in the future hopefully will offer better opportunities to develop prophylactic measures, e.g. an effective open access endoscopy service The world experience demonstrates effectiveness of non-surgical treatment that could reduce the number of bleeding peptic ulcer patients Finally, the cost-effectiveness of this approach is evident

DNA ploidy in gastric cancer: does it predict clinical behaviour?

J.M. Mugüerza, A. López, A. Gutiérrez, M. Díez, A. Martín, I. Lasa, E. Tobaruela, P. Hernández, J A.L. Asenjo, P. Domínguez, F. Noguerales and J. Granell *Servicio de Cirugía General, Hospital Universitario Príncipe de Asturias, Carretera de Alcalá-Meco s/n, Alcalá de Henares, 28805 Madrid, Spain*

Cytometric studies have demonstrated that human tumours are characterized by karyotypic abnormalities. DNA content has been proposed as an indicator of outcome in several neoplasms and may reflect its biological behaviour. The aim of this study is to relate DNA features to clinical course in patients with gastric cancer.
Patients and methods: Sixty-eight patients operated on for gastric adenocarcinoma were analysed. They were staged according to the Japanese Society for Research in Gastric Cancer (JSRGC) as follows: Stage I 13 (19 per cent), II 2, II 32 (47 per cent), IV 21 (31 per cent). Thirty-two were submitted to total and 35 to subtotal gastrectomy, with 29 R1 lymphadenectomy (43 per cent), 30 R2 (45 per cent) and 8 R3 (12 per cent). In 41 patients (61 per cent) the operation was performed with curative intent meeting the JSRGC society criteria (complete removal of the tumour and node level involvement less or equal to the lymphadenectomy level performed). Global 3-year actuarial survival was 50 per cent, and 80 per cent considering only the patients submitted to potentially curative resections. The DNA characteristics were obtained by flow cytometry techniques from paraffin embedded samples.
Results: Twenty-three out of 68 tumours were considered aneuploid (33 per cent). Ploidy distribution by stage was: stage I (3 Aneuploid/10 Diploid), II (0A/2D), III (8A/24D), IV (12A/9D). Aneuploidy was found in 9/41 patients (21 per cent) submitted to curative surgery and 14/26 (53 per cent) to non-radical procedures ($P < 0{\cdot}05$). With respect to histological type 12/43 intestinal (27 per cent) and 11/25 diffuse tumours (44 per cent) were aneuploid ($P = 0{\cdot}08$). Global 3-year actuarial survival was 27 per cent for the aneuploid group and 63 per cent for the diploid group ($P < 0{\cdot}001$) Ploidy maintained its prognostic significance when only patients operated with curative intent were considered: 3-year actuarial survival 46 per cent for the aneuploid group and 85 per cent for the diploid group ($P < 0{\cdot}03$).
Conclusions: Aneuploidy has an adverse prognostic value both in the global series and in completely resected gastric cancer with curative intent, and could play a role in the selection of high-risk patients in order to include them in adjuvant therapy trials.

Multiple lesions: an aggravating factor in gastroduodenal ulcer

R. Nemeş, F. Ghelase, I. Georgescu and L. Chiuţu *Clinical Hospital Nr. 1, Surgical Clinic I, 60 Mareşal Antonescu Street, Craiova, Romania*

Aim: The aetiopathological, clinical and therapeutical study of multiple gastroduodenal ulcers.
Material and methods: One hundred and forty-two (8·8 per cent) multiple gastroduodenal ulcers from 1160 gastric and duodenal ulcers admitted in the latest 5 years (1989–1993) are analysed. Aetiopathogenity. more than 65 per cent of the cases had a family history of peptic ulcer disease, Group 0 28·5 per cent, professional noxis 16 per cent and unprofessional noxis 76·5 per cent (tobacco, alcohol, coffee) Macroscopically there were three topographic forms: multiple duodenal ulcer 86 cases (60·6 per cent); multiple gastric ulcers 15 cases (10·5 per cent) and multiple gastroduodenal ulcers in 48 cases (28·8 per cent) Clinical characteristic features included long-term evolution marked by complications of haemorrhage in 65 cases (66·2 per cent), perforation in 34 cases (57·7 per cent), multiple complications in 85 cases (66·2 per cent). The principal clinical aspect is that the preoperative diagnosis of multicentricity is difficult to establish (42·8 per cent). Treatment comprised 137 operated cases (96·7 per cent) with two main approaches: operations that treated only the complication (20 cases) and operations that resolve the complication and remove all the ulcerous lesions (117 cases)

Results: One hundred and twenty-five cases (86 per cent) had fair evolution; 17 cases general or/and local complications (anastomosis fistula, upper gastrointestinal bleeding, jaundice through obstruction, infarction); six cases required reoperation, general mortality· 5·4 per cent, postoperative mortality: 4·9 per cent.

Conclusions: The defining features of the multiple gastroduodenal ulcers are as follows: (a) it occurs with patients with long clinical suffering (55·3 per cent); (b) almost all are complicated (93·7 per cent), with two or more complications in over 50 per cent of the cases; (c) the clinical aspect is that of the main complication; (d) the preoperative diagnosis is established in less than 50 per cent of cases; (e) the treatment is surgical (97 per cent), with two main approaches: the treatment of the complication only or the removal of all ulcerous lesions.

Perforated duodenal ulcer: analysis of aetiopathogenic, clinical and risk factors

J.R. Nuñez, C. Martinez-Ramos, T. Jorgensen, R. Sanz, M.R Gopegui, L. Pastor, C. Pérez and S. Tamames *San Carlos University Hospital, Ciudad Universitaria, 28040 Madrid, Spain*

We studied 109 patients that underwent surgery for perforated peptic ulcer between 1983 and 1994. 84 per cent ($n = 91$) were males, with a mean age of 52 years (17–93 years) With respect to the season of the year in which the perforation took place, 28 per cent ($n = 30$) happened in spring, 30 per cent ($n = 32$) in summer, 17 per cent ($n = 18$) in autumn and 27 per cent ($n = 29$) in winter. Thirty-three per cent ($n = 36$) smoked and 17 per cent ($n = 19$) referred previous ulcer symptoms Mean elasped time between beginning of symptoms and admission to hospital was of 4 7h (1–72h); 93 per cent ($n = 101$) of patients showed the characteristic clinical presentation of perforated peptic ulcer and in 7 per cent ($n = 8$) the clinical presentation was not characteristic. Sixteen per cent were in shock at the time of admission. Radiological study revealed pneumoperitoneum in 68 per cent ($n = 74$) and 76 per cent ($n = 82$) of patients presented leucocytosis (>10 000/mm^3). Diffuse peritonitis was present at surgery in 95 per cent ($n = 103$), while it was localized in the remaining 5 per cent ($n = 6$). Perforation was duodenal in 94 per cent ($n = 102$) and gastric in the remaining 6 per cent. In 50 per cent ($n = 55$) of patients a provisional surgical treatment was performed, suture and epipoplasty (S + E) and in the other 50 per cent a definitive treatment was performed, truncal vagotomy and pyloroplasty (TV + P) in 91 per cent ($n = 50$), and gastrectomy (G) in 9 per cent ($n = 5$). Operative mortality was 8 per cent ($n = 9$) Of these S + E was performed in eight patients (89 per cent) and TV + P in one patient (11 per cent) We have analysed the relation between the following factors age, previous ulcer symptoms, associated diseases, preoperative time, shock, ulcer location, surgical treatment modality and mortality. The results show that there is no relation of the surgical treatment modality with age, ulcer location nor shock. There is a significant relation respect to the performance of a definitive surgical treatment which is more frequent in patients with previous ulcer symptoms ($P < 0{\cdot}05$) in patients and in which the preoperative time was less than 8h ($P < 0{\cdot}05$). The surgical treatment modality was also significantly related to the presence of associated diseases, with a provisional surgical treatment being preferred in these patients. With respect to mortality, no significant relation was observed with ulcer location, shock, nor preoperative time. Mortality is significantly related with age above 60 years ($P < 0{\cdot}05$), with no previous ulcer symptoms ($P < 0{\cdot}05$) and with the presence of associated diseases ($P < 0{\cdot}05$) Finally, the surgical treatment modality is significantly related with mortality being higher in those patients in which a provisional surgical treatment (S + E) was performed, noting that these patients have a significant relation with the existence of associated diseases.

Results of palliative surgery for stomach cancer: multivariate analysis of 305 patients

F. Pacelli, G.B. Doglietto, S. Alfieri, M. Malerba, C. Carriero, G. Devivo, P. Caprino and F. Crucitti *Department of Surgery, Catholic University, Rome, Italy*

During the period 1981–1995, 305 (48·4 per cent) of 628 consecutively admitted patients at our unit for stomach cancer did not undergo radical resection because of the local and/or distant spread of the disease 93 gastric resections (GR) including 38 total gastrectomies and 55 subtotal gastrectomies, 78 bypass procedures (BPP), 72 explorative laparotomies (EL) and 62 no operations (NO).

Five-year survival (excluding 22 patients with positive N3 nodes which have, in our experience, a prognosis similar to radical operation) and postoperative mortality resulted in 13·1 per cent and 11·8 per cent, 2·4 per cent and 8·3 per cent, 4·9 per cent and 10·2 per cent, 0 and 6·4 per cent after GR, EL, BPP and NO, respectively. A uni- and multivariate survival analysis according to Cox model was performed including the following variables (age, sex, Lauren histological type, Bormann classification, location and spread of the tumour and the type of operation) only the extent of tumour spread (local *vs* distant $P = 0{\cdot}03$) and the type of operation (GR *vs* BPP, EL, NO· $P = 0{\cdot}001$) turned out to be independently associated with survival.

The study indicates that resectional surgery should be undertaken whenever possible in patients with far advanced stomach cancer as a significant survival advantage is demonstrated, when computed axial tomography or laparoscopy anticipated that any surgical palliation is not possible, it is better to avoid explorative laparotomy in order to avoid operative mortality. In patients with unresectable obstructing tumours, bypass procedures are suggested in order to counteract the negative oncological effects of malnutrition.

Gastric surgery does not increase the prevalance of Barrett's oesophagus: a retrospective study

P. Parrilla, F. Martínez de Haro Luisa and A. Ortiz
Department of General Surgery, University Hospital Virgen de la Arrixaca, El Palmar, 30120 Murcia, Spain

Aim: To compare the prevalence of Barrett's oesophagus (BO) in patients with an intact stomach and patients with an operated stomach in order to assess the importance of biliary reflux in the genesis of BO

Patients and methods: A total of 22 236 upper digestive endoscopy reports were reviewed and classified into two groups. intact stomach ($n = 21\,023$) and operated stomach ($n = 1213$), which in turn was divided into five subgroups according to surgical techniques: bilateral truncal vagotomy plus pyloroplasty ($n = 444$ cases), distal partial gastric resection of varying amplitudes with gastrojejunostomy (Billroth II) ($n = 445$ cases), distal partial gastric resection of varying amplitudes with gastroduodenostomy (Billroth I) ($n = 211$ cases); bilateral truncal vagotomy plus gastrojejunostomy ($n = 59$ cases) and total gastrectomy with Roux-en-Y gastrojejunostomy ($n = 54$ cases) The median time between surgery and endoscopy was 5 years (range 1·14 years), 2 5 years (range 0 5–15 years), 3 years (range 0·5–13 years), 6 years (range 2–16 years) and 1·5 years (range 0·5–10 years) in each of the groups, respectively The percentage of the total patients with oesophagitis, percentage of the oesophagitis patients with Barrett's oesophagus and percentage of the Barrett's oesophagus patients with complications in each of the groups were calculated Comparison was made using the χ^2 test.

Results: Oesophagitis is more common in patients with an intact stomach than in the operated stomach group. Patients with Barrett's oesophagus had more frequently undergone surgery than those patients with an intact stomach, although the differences were not statistically significant

Conclusions: Although we recognize the methodological limitations of this study, our results suggest that previous gastric surgery, despite increased duodenogastric reflux, does not modify the prevalence of Barrett's oesophagus in patients with oesophagitis.

Endoscopic congo red test (ECRT) and recurrent ulcer during a 12–17-year follow-up period after vagotomy

M. Peetsalu, T. Vardja and A. Peetsalu *Department of Surgery, University of Tartu, Puusepa 8, Tartu EE2400, Estonia*

Aim: To document the change in ECRT with time following vagotomy performed for duodenal ulcer (DU), and to correlate these changes with ulcer recurrence

Materials and methods: One hundred and twenty-eight consecutive vagotomies were carried out for DU between 1976 and 1983: 27 truncal vagotomy with pyloroplasty and 101 proximal vagotomy, 19 without drainage and 82 with drainage (pyloroplasty 59, duodenoplasty 11, Jaboulay gastroduodenostomy 12). All patients were gastroscoped at an average of 9 (7–12) years and again 14 (12–17) years after surgery The presence of recurrent DU was documented and completeness of vagotomy assessed simultaneously by ECRT Incomplete vagotomy (ICV) was diagnosed by positive ECRT of the gastric corpus mucosa, and classifed as small (one or more areas 1–30mm in diameter) or large (20 per cent or more of the gastric corpus mucosa involved, subjective assessment).

Results: There were no recurrences in patients with complete vagotomy Recurrence rate in patients with ICV rose from 52 per cent (67/128) at 9 years to 70 per cent (90/128) at 14 ($P < 0\cdot05$) and the proportion of large recurrences were 12 per cent (8/67) and 32 per cent (29/90) respectively ($P < 0\cdot05$). All patients with ICV at 9 years had ICV at 14 years Recurrent DU rate rose from 4 per cent (5/128) to 18 per cent (23/128) ($P < 0\cdot05$) and was five times higher in patients with large than small ICV, at both assessment times 5 per cent (3/59) *vs* 25 per cent (2/8) and 11 per cent (7/61) *vs* 55 per cent (16/29), respectively Of the 23 recurrences at 14 years, only six (26 per cent) were asymptomatic

Conclusions: After vagotomy the incidence of ICV as determined by ECRT rises with time Recurrent DU rises with time and is limited to patients with ICV, correlating with ICV extent. Where vagotomy remains complete by ECRT, recurrent DU is unlikely

Gastric angiodysplasia

A. Popovici, C.N. Popa and F. Proinov Jr. *Clinic of General Surgery, Clinical Hospital Fundeni, The University of Medicine and Pharmacy 'Carol Davila', Bucharest, Romania*

Gastric angiodysplasia (GA) is a rare cause of upper gastrointestinal haemorrhages (UGH). Between 1981 and 1995 from 39 patients with various digestive angiodysplasia, seven (18 per cent) presented a gastric site (+ jejunal in two cases). Four patients (57 per cent) were under 30 years old. UGH was the first clinical symptom in six cases, without a previous digestive illness (first episode in five and recurrent in one); for one patient operated on for a giant-penetrating gastric ulcer, the diagnosis was established only on postoperative histology The preoperative diagnosis was not made endoscopically, the main supposition was haemorrhagic gastritis ($n = 5$); angiography suggested GA in two cases. The postoperative histological examination established the diagnosis in all cases. One case (11 years old) caused the antral lesion called 'water melon stomach' but in reality was a diffuse GA. Two patients died: one with a congenital portal hypertension and one with gastric ulcer. Haemorrhage dictated surgical treatment in six patients. The seven patients collectively required 15 operations: nine for haemostasis, two for other concomitant illnesses and four for postoperative complications. Some operations were unspecific, the real aetiology of the haemorrhage being unrecognized The postoperative morbidity included five episodes of recurrent haemorrhage and two septic complications, two patients (28·5 per cent) died with septic shock. GA is a possible cause of UGH, specially in young patients, when the diagnosis is not certain The only certain means of diagnosis is postoperative histological examination of resected tissue.

The value of clinical and endoscopic signs in prediction of recurrent bleeding from gastroduodenal ulcer

J. Pundzius *Surgery Clinic, Kaunas Medical Academy, Mickevičiaus 9, Kaunas, 3000, Lithuania*

Aim: To determine which clinical, laboratory and endoscopic signs are mostly informative in prediction of recurrent bleeding from gastroduodenal ulceration.

Materials and methods: Nine hundred and forty-nine patients with peptic ulcer haemorrhage were treated in the Surgery Clinic of Kaunas Academy Clinics during a 10-year period Early endoscopy was performed on 95 1 per cent of patients Endoscopic haemostasis (mono- or bipolar coagulation, laser and injection therapy) was given in 659 cases and bleeding was controlled in 96·2 per cent. Rebleeding occurred in 75 cases (main group) Control group included 100 patients, who had no recurrent bleeding. EPIINFO and BMDP Statistical Package was used for the two-step computer analysis of 59 variables of patients of both groups

Results: Twelve parameters predictive for rebleeding were identified and correlation coefficients calculated These were frequency and character of haematemesis, the shortest duration between two episodes of bleeding at home, shock index at admission, rate of decrease in Hb level, endoscopic view of ulcer basis, ulcer type and area, its complications, patient's sex and associated diseases. A computer system to predict recurrent bleeding was created using a Cox's regression model based upon coefficients of selected variables. The accuracy of the system was shown to be 58·3 per cent, and the sensitivity in the high risk group 74·6 per cent. This system has allowed us to improve the management of patients with bleeding peptic ulcer during 1992–93 and to decrease the rebleeding rate to 7 4 per cent, with mortality 3·4 per cent (*vs* 6·5 per cent during 1982–91; $P < 0\ 05$).

Investigation of experimental bleeding: initial control with injective haemostatics

J. Pundzius and M. Jievaltas *Surgery Clinic of Kaunas Medical Academy, Mickevičiaus 9, 3000 Kaunas, Lithuania*

The study's aim was to determine the effect and differences between various endoscopic injective haemostatics in achieving initial control of experimental gastrointestinal bleeding.

Acute experiments were carried out in 11 dogs. Laparotomy and anterior gastrotomy were performed After heparinization 203 acute experimental bleeding ulcers were made in the stomach. Bleeding ulcers were treated with injections of 1 ml adrenaline 0·1 per cent, ethanol 96 per cent, polidocanol 1 per cent, thrombin, ornipressin, NaCl 10 per cent solutions.

Thirty-five experimental ulcers (EU) were treated with adrenaline and initial bleeding control was achieved in 30 ulcers (85·7 per cent), 43EU and 33 (76·7 per cent) initial control of bleeding using ethanol, 30EU and 23 (76·6 per cent) initial control of bleeding for polidocanol, 35EU and 26 (74·3 per cent) initial control of bleeding for thrombin, 30EU and 23 (76·6 per cent) initial control of bleeding for ornipressin, 30EU and 24 (80 per cent) initial control of bleeding for NaCl.

Conclusion: results did not show significant ($\chi^2 = 1\cdot43$) differences among investigated endoscopic injective haemostatics in achieving initial bleeding control.

The value of 'early operation' for gastro-duodenal peptic ulcer

D. Radovanovic, J. Kalaba, B. Vekic, A. Bajec, D. Matijasevic and I. Pavlovic *KBC 'Dr D. Misovic' Surgical Clinic, Milana Tepica 1, Belgrade, Yugoslavia*

Aim: The aim of this study is to evaluate the role for data for early (24–48h) elective operation for peptic ulcer haemorrhage. It is important to define factors which predispose to massive haemorrhage We examined age, weight, number of haemorrhage episodes and duration of anaemia as factors which made patients susceptible to future massive ulcer haemorrhage. These factors can help us to choose patients for an early or elective operation where the ulcer is not currently bleeding

Material and methods: This study includes 58 patients who were operated on for bleeding peptic ulcer of stomach or duodenum in 6-year period (1990–95). After admission to hospital all patients were examined by fibre-optic endoscopy. All of them had suffered serious blood loss due to abundant arterial haemorrhage from peptic ulcers (Forrest I).

Results: Thirty-five patients (60·34 per cent) with duodenal ulcer (DU) and 23 (39·66 per cent) with gastric ulcer (GU) underwent surgery. Primary ulcer haemorrhage is cause for operation in 36 (62·07 per cent), recurrent haemorrhage in 22 (37·93 per cent) Forty-eight of those undergoing operation (82·67 per cent) were older than 50 years, and 27 (46·55 per cent) were older than 60 The number of previous haemorrhagic episodes was important in 31 (53·45 per cent) According to Nagao criteria 55 (94·83 per cent) had massive haemorrhage preoperatively Forty-five (77·58 per cent) had a peptic ulcer history longer than 6 years

Conclusions: Besides morphological characteristics of peptic ulcer, factors which contribute to our indications for early elective operation for bleeding peptic ulcers are (a) age older than 60 years, (b) the first episode of massive bleeding, (c) number of previous bleeding episodes (3 and more), (d) duration of peptic ulcer history (5 years and more)

Gastric cardia carinoma: the Oporto cancer centre experience

M. Serralva, V. Garrido, T. Mesquita, A Ramalho,
D. Gonçalves, G. Santos, V. Veloso and C. Silva *Instituto Português de Oncologia, Centro Norte, Porto, Portugal*

Aim: Cardia carcinoma seems to be a distinct clinical entity when compared with the tumours from other stomach sites This study was performed to identify the clinical and pathological characteristics of this tumour and analysed the overall 5-year survival in these patients

Patients and methods: From January 1974 to December 1995, 1339 patients were operated on with gastric cancer in our Institution, of which 120 (9 per cent) had the tumour localized at the level of gastroesophageal junction (cardia) Eighty-five (71 per cent) patients were men and 35 (29 per cent) were women, with an average age of 65·5 ± 10·5 years (range 36–87 years) with a ratio male female of 2·4·1. The mean time of presenting complaints was 6·5 ± 4·8 months and the most common complaints were dysphagia (73 per cent), anorexia/weight loss (62·5 per cent), epigastric pain and postprandial fullness (44 per cent) In 15 (12·5 per cent) patients, dysphagia was the only complaint. In 39 (32·5 per cent) patients the diagnosis was made with contrast radiographic examination and in 75 (62·5 per cent) endoscopically. Endoscopic biopsies were performed in 113 patients Surgical curative resection (R0) was performed in 57 (47·5 per cent) patients, 22 (18·3 per cent) had palliative surgery (R1–2) and 41 (34·2 per cent) had exploratory laparotomy The histological study revealed a predominance of moderately differentiated forms (36·5 per cent). In TNM classification (AJCC), four (3 per cent) patients belonged to stage I, 18 (15 per cent) to stage II, 50 (42 per cent) to stage III and 48 (40 per cent) to stage IV. Forty-four (37 per cent) patients were submitted to adjuvant chemotherapy

Results: Of tumours 65·8 per cent were resectable with cure possible for 42·5 per cent Seventeen patients had postoperative complications (morbidity rate 14 per cent) The operative mortality rate was 7·5 per cent The average length of hospital stay was 14 days The average survival was 13·8 months and the average follow-up was 15·7 months (range 2–80 months) The overall 5-year survival rate (actuarial method) was 9·7 per cent.

Conclusions: Cardia carcinoma is an aggressive neoplasia that occurs predominantly in the male, is diagnosed at an advanced stage (80 per cent in stages III/IV) and has a poor overall 5-year survival Early detection is crucial for improving the survival in these patients

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Selective proximal vagotomy and duodenoplasty in treatment of postbular ulcer stenosis

S. Shterev, B. Kornovski and D. Dobrev *Medical University Varna, 9002 Marin Drinov str. 55, Varna, Bulgaria*

During the period 1990–1995 a total of 104 patients were operated on for pyloro-duodenal ulcer. Forty-two of them were treated by Billroth I stomach resection, 15 were treated by Billroth II resection, in 10 of the patients excision was undertaken together with pyloroplasty and truncal vagotomy, and in 37 cases the stenosis was postbulbar which helped us to perform a selective proximal vagotomy (SP) + duodenoplasty The patients group included 25 men and 13 women aged from 17 to 65 years. We had no early postoperative complications. We achieved excellent results in all patients with restoration of the alimentary passage; further examination of the patients showed 25 excellent, nine very good and three good later results

Based on the results of our treatment for complicated pyloro-duodenal ulcers we concluded that SPV together with duodenoplasty is the method of choice for stenotic postbulbar ulcers preserving pylorus function and avoiding duodeno-gastric reflux, and alcaline reflux-gastritis, respectively

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Perforated pyloric ulcer inside the left chest through diaphragmatic hernia

J.M.B. Sousa *Hospital de S. José, 4820 Fafe, Portugal*

The author presents a rare case of perforated pyloric ulcer and emphasizes the clinical features, diagnosis and surgical treatment. A 38-year-old male had been in a traffic accident 15 years earlier, from which had arisen a left diaphragmatic hernia. He had not undergone surgery. On presenting at the hospital with abdominal-chest pain, the chest X-ray showed the presence of the levyne tube inside the left chest, confirming the hypothesis of diaphragmatic hernia. The leak of contrast through the levyne tube led to the diagnosis of a perforated viscus inside the left chest Exploratory laparotomy was performed and the diaphragmatic hernia was seen to contain some small bowel loops, the splenic flexure of the colon, and the stomach with perforated pyloric ulcer, from where the contrast was leaking. Reduction of the hernia contents was performed, truncal vagotomy with Heineck-Mickulicz pyloroplasty and suture of the diaphragmatic defect was achieved with non-absorbable material. Lavage and drainage was performed of the abdominal cavity as well as the left chest. The patient was discharged from hospital at 21 days

Conclusions: In the absence of sophisticated diagnostic techniques such as CT scan or echography, contrast X-ray studies were important to define the herniation and to make the diagnosis in this case

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Value of continuous intraluminal aspiration by double lumen catheter in complicated duodenal fistulas

A Tanik, T Kale, M A. Kuzu, B. Bostancı and M. Özmen
Department of Surgery, Ankara Numune Hastanesi, Turkey

Duodenal fistula has a high morbidity and mortality rate due to uncontrolled sepsis, high output, malnutrition and multiple operations In order to avoid these complications, we report a modified approach to the conservative management of complicated duodenal fistulas This technique has been used successfully in the treatment of four patients [mean age 42 (26–56) years] with duodenal fistula, who were treated (two duodenal stump failure, one following D3 gastric resection for carcinoma, one following Billroth II gastric resection for bleeding peptic ulcer) or referred to our unit (one post-pyloroplasty and following duodenal repair for trauma). Three of these cases had undergone a second operation for either fistula repair or for its complications, but the fistula failed to close In all cases fistula was visualized by gastrograffin studies. Although these patients had classical single lumen nasogastric tube before the insertion of double lumen catheter, the output of fistulas was not decreased Therefore, the double lumen catheter was inserted to the level of the fistula under endoscopic control The output of fistula was significantly decreased on the first day following the intraluminal continuous aspiration [the mean duodeno-cutaneous fistula output was 2050 (1300–2700) ml before the double lumen catheter insertion *vs* 707 (180–1500) ml after, $P < 0.01$] and continued to decrease progressively thereafter The mean time for fistula closure was 13 (12–15) days. All patients had uneventful recovery.

We conclude that this modified technique might be useful in the conservative treatment of complicated duodenal fistulas

Helicobacter pyloridis in duodenal ulcer: triple therapy *vs* omeprazole plus amoxycillin therapy

S. Yıldırım, A. Baykan and M. Ozdemir *Şişli Etfal Teaching State Hospital, Ist Surgical Department, Istanbul, Turkey*

Three hundred and fifty patients with duodenal ulcer underwent upper endoscopy between February 1992 and March 1996 and antral biopsies for *H. pylori* examination were taken. Of the patients 98 per cent ($n = 343$) were found to have positive results. Of these patients 230 (70 per cent) were given triple therapy (colloidal bismuth subcitrate 3 × 600mg, metronidazole 3 × 250mg, amoxycillin 4 × 500mg) for 2 weeks and 113 (30 per cent) were treated with omeprazole (2 × 40mg) plus amoxycillin (4 × 500mg) for 2 weeks All patients were called for re-endoscopy after 2 weeks, 2 months and 7 months, and antral samples obtained for *H. pylori* In the first group 79, 71, 68 per cent were negative after 2 weeks, 2 and 7 months, respectively. For the second group the rate of negative rates were 68, 43, and 14 per cent after 2 weeks, 2 months and 7 months, respectively.

In conclusion, neither modality was found to eradicate *H. pylori* in the antrum, and triple therapy found to be significantly more effective in terms of abolishing *H pylori* from antrum and sustaining this status.

Surgical approach of gastric cancer in relation to tumour site

P. Zairis, L. Iosephidis, R. Nafas, G. Constantinidis, G. Verycocacis, S. Prigouris, A. Portinos and J. Poulantzas *4th Surgical Department of 'Evangelismos' Hospital, 45–47 Ypsilantou Str., Athens, Greece*

Aim: To present our experience of the management of gastric cancer in relation to the site of the tumour

Patients and methods: Between January 1986 and December 1995, 349 patients underwent surgery for gastric carcinoma. They were 226 men and 123 women (M/F ratio: 1·84/1), with a mean age of 64·5 years. Preoperative resectabiity was assessed with upper gastrointestinal series, computed tomography, endoscopy and more recently in several cases endoscopic ultrasound was used. Carcinomas were located in the upper third of the stomach in 58 cases (16·6 per cent), in the middle third in 110 cases (31·5 per cent) and in the lower third in 181 cases (51·9 per cent). In the upper third cases, 41 patients (70·7 per cent) underwent resection which was subtotal gastrectomy and splenectomy in 17 cases, total gastrectomy, and splenectomy in 10 cases and total gastrectomy alone in 14 cases. Seventeen patients (29·3 per cent) underwent either bypass procedures or biopsy alone for unresectable carcinoma. In the middle third cases, 84 patients (76·4 per cent) underwent resection which was total gastrectomy and splenectomy in 28 cases, total gastrectomy alone in 18 cases. Billroth II subtotal gastrectomy in 29 cases and Billroth I subtotal gastrectomy in nine cases. Twenty-six patients (23·6 per cent) underwent biopsy or bypass surgery In the lower third 169 patients (93·3 per cent) underwent resection which was total gastrectomy in six cases, Billroth II subtotal gastrectomy in 156 cases and Billroth I subtotal gastrectomy in seven cases. Twelve patients (6·7 per cent) underwent biopsy or bypass procedures. As for the extent of lymph node clearance R2 dissection has become recently the procedure of choice.

Conclusions: Total or subtotal gastrectomy is the procedure of choice for upper third lesions whereas subtotal gastrectomy is the resection of choice for middle or lower third lesions. R2 lymph node dissection should be applied as surgical morbidity and mortality are not affected.

General

Splenectomy for chronic thrombocytopenic purpura: report of 64 cases

O. Armstrong, M D Leclair, E. Letessier and J.-C. Le Néel *Clinique Chirurgicale A, CHU Hôtel-Dieu, 44035 Nantes Cedex 01, France*

Aim: The aim of this retrospective study was to evaluate the early and late results of splenectomy in case of chronic thrombocytopenic purpura.
Methods: Between 1985 and December 1994, 64 patients underwent splenectomy for chronic thrombocytopenic purpura (CTP) Sex ratio was 1.1. Mean patient age was 42 years old Prior steroid treatment had been used in 91 per cent. Patients were referred for splenectomy because of the failure of the medical therapy, or for HIV-associated immune thrombocytopenia purpura (n = 6 per cent) In the former group, patients had either responded but relapsed when doses were reduced (n = 42 per cent) or refractory to corticosteroids (n = 39 per cent). All patients received polyvalent pneumococcal vaccination before splenectomy. All patients were followed up. Haematological results were assessed using Berchtold's response criteria 3 months after splenectomy and at the end of the study.
Results: Postoperative complications occurred in seven cases (11 per cent). One patient developed postoperative pancreatitis, underwent left pancreatectomy and died at day 21 Mean patient follow-up was 50 months (range 3–118 months). No overwhelming post-splenectomy infection occurred during the follow-up period. Response rates at 4 years were complete response in 76 per cent, partial response in 14 per cent, and failure in 11 per cent In case of complete response at 3 months, final response rate at 4 years was 94 per cent.
Conclusions: In our experience no preoperative factor can predict the response rate of CTP to splenectomy. Postoperatively, early increase in the platelet count, as well as a good response at the third month are associated with beneficial response to splenectomy.

Ambulatory surgery in a community hospital: patient satisfaction and quality care survey

J.M. Badia, M. Prats, L.A Hidalgo, J Carbonell and J.M. Gubern *Department of Surgery, Consorci Sanitari de Mataró, Lepant 13, 08301 Mataró, Barcelona, Spain*

Nowadays healthcare professionals are aware that quality of care ought to be assured. The knowledge of main quality indicators should be relevant to evaluate an ambulatory surgery programme.
Aim: The early outcome of surgical procedures performed and the patients' satisfaction of an Ambulatory Surgery Unit (ASU) in a community hospital were analysed
Methods: Hospital admissions, emergency phone calls, a first postoperative day phone survey and a mail questionnaire were recorded At 6 and 12 months after the beginning of the programme, the surgeons participating in it completed an anonymous questionnaire about the ASU performance and their level of acceptance of ambulatory surgery.
Results: (a) Patients: From June 1994 to December 1995, 1592 patients were operated in the ASU Forty patients (3 per cent) had to be admitted on the same day as the operation. In 5 per cent of cases the patient made a postoperative emergency telephone consultation. In the early phone satisfaction survey, outcome at 24 h was considered good by the patient in 836 cases (86 per cent) The mail questionnaire was completed by the patient 2 weeks after the operation in 21 per cent of cases Moderate pain was the main claim of patients in the questionnaires received (21 per cent), followed by minor haemorrhage (3 per cent) In 86 per cent of cases the patients deemed the overall service given in the ASU was good or excellent. Ninety-five per cent of the patients would use again the services of the ASU

(b) Staff surgeons· Twenty-six surgeons answered a written anonymous questionnaire at 6 and 12 months after the beginning of the programme Mean evaluation of the ASU performance (limits 0–10) rose from 6·8 ± 1·9 at 6 months to 7·7 ± 1·2 at 12 months (P = 0·025). The level of acceptance of ambulatory surgery remained unmodified at a mean of 8·3 ± 1·2 during the study. Substitution index and the level of utilization of the ASU differed substantially among the surgeons.
Conclusions: Satisfaction level of the operated patients in the ASU was good overall. The main detected problem was pain control after discharge. Staff satisfaction level is also good, but different utilization patterns of the ASU have been observed among the surgeons

Excision of submaxillary gland: our experience (1970–1995)

M. Biffoni, M. Marchesi, G. Nuccio, P Picchi, F. Tartaglia and F.P. Campana *General Surgery, University of Rome 'La Sapienza', Policlinico Umberto I, Viale Regina Elena 324, 00161, Rome, Italy*

Submandibular gland excision is proposed in the treatment of neoplastic and non-neoplastic diseases, this surgical procedure can be performed by transoral or transcervical approach. The aim of the study is to demonstrate that cervical approach must be preferred because it is safer and provides a wider surgical exposure.

From 1970 to June 1994, 54 patients (47 with chronic sialadenitis, seven with benign tumours and seven with malign tumours) were submitted to excision of the submaxillary gland. Of the 54 resections performed, two were completed with 'functional' cervical lymphadenectomy and one with radical neck dissection, in patients with malignant neoplasms There were no postoperative deaths; complications occurred in one patient (1/54 = 1·8 per cent), with iatrogenic permanent lesion of the maxillary branch of the facial nerve (0/47 patients with benign diseases and 1/7 (14·7 per cent) patients with malignant diseases) The cervical approach for the resection of the submaxillary gland is preferred to the transoral approach because of a lower risk of iatrogenic lesions of the lingual and hypoglosssal nerves and the possibility of a curative resection in case of malignant neoplasms; with a controlled and tested technique, the risk of a lesion of the maxillary branch of the facial nerve is also reduced with the cervical approach.

False acute abdomen in emergency surgery

P. Blidaru, A. Blidaru and G. Popa *Spitalul Clinic de Urgenta Floreasca, Calea Floreasca no. 8, Bucharest, Romania*

False acute abdomen (FAA) is a clinical reality that, disguised as a surgical acute abdomen, is the cause of useless surgical operations that sometimes have a fatal outcome. This paper is a retrospective study with prospective implications, regarding the patients with acute abdomen operated on between 1960 and 1993 in the Emergency Hospital Floreasca from Bucharest Of these, in 488 (0·65 per cent) of the cases no cause for the clinical presentation was found (FAA) 'negative laparotomy'. The diagnosis can be altered by an agitated, anxious, patient that amplifies his clinical picture, and/or by a doctor that examines the patient hurriedly, without considering other laboratory tests, and without asking the advice of a senior colleague. The diseases that determined FAA can be classified as. (a) systemic diseases with abdominal manifestation (59 per cent) (intoxications, infectious diseases, CNS diseases, endocrine, allergic diseases, etc), (b) diseases of the nearby organs having abdominal manifestation (27 per cent) (cardiac and pulmonary diseases, lesions of the thoracic wall or of the vertebral column), (c) abdominal diseases but without operative indication (14 per cent) (tabes dorsalis, diabetes mellitus, painful hepato-splenomegaly, nephro-ureteric colic, paralytic ileus, pyelonephritis, etc).

The age of the patients varied between 16 and 89 years, with a mortality of 17 per cent. Acute myocardial infarction, leptospirosis, basal pneumonias, renal failure have disguised themselves as an acute abdomen, and represent the cause of most of the deaths The limit between FAA and a true acute abdomen cannot be always traced completely, in spite of a correct clinical examination or of the laboratory tests.

In our opinion a patient suspected of having FAA has to be admitted and kept under strict medical observation Emergency laparotomy or laparoscopy remains a method of diagnosis that may be sometimes postponed due to uncertainty, but produces the certainty of a pathology report.

Intestinal obstruction from post-laparotomy hernia and peritoneal mesothelioma

D Cerbone, P. Esposito, G. Cione, A. Sorge and
G. Cerbone *Department of Surgery, University Federico II and Department of Emergency, New Pellegrini Hospital, Naples, Italy*

The clinical case reported describes an acute clinical onset of intestinal obstruction for abdominal post-laparotomy hernia and malignant mesothelioma without ascites formation An 85-year-old male presented with abdominal pain for 4–5 days. His past history included prostatectomy via laparotomy about 10 years prior for benign disease; an uncomplicated right inguinal herniectomy for external oblique hernia. Physical examination showed fair general condition. Abdomen was distended and aching diffusely; there were two scars due to previous operations At the paramedian hypogastric situs, a hard tumefaction was noted, the size of an orange, non-reducible and painful upon palpation. Peristalsis was absent, diffuse Blumberg throughout the abdomen. Rectal examination negative The following emergency tests were performed. (a) blood chemistry — no evidence of relevant alterations, (b) blood gas analysis and base acid balance, within normal limits; (c) direct abdomen radiography revealed a relevant dilatation of intestinal loops located in the mid-abdomen Surgical intervention was performed. The macroscopic picture indicated marked dilatation of the colon, because the obstruction of a subumbilical, laparocoelic cavity occupying the greater omentum with small intestine, and the sigmoid undergoing anterior parietal cicatricial fusion. It was also noted that the intestinal loops, mesentery and parietal serosa were disseminated by small, lenticular formations, that, at examination, resulted as a mesothelioma. There was no free liquid in the abdomen The causes of the obstruction were resolved and the patient was discharged on postoperative day 20 with canalized alvus and apyrexia. Today the patient is alive. Peritoneal mesothelioma is a rare disease correlated with asbestos exposure. A frequently fatal disease, it is very difficult to diagnose· the only secure form of diagnosis is through laparotomy and histological macro-biopsies.

Malnutrition

M. Chiaretti, G. Marenga and P. Catania *Emergency Surgery Department, 'La Sapienza' University, Rome, Italy*

Man survives environmental attacks if he is able to adapt to what surrounds him and if he is able to react to it protecting his integrity. The adaptation to environment consists essentially in the synthesis of proteins for which there is a need: energy, aminoacids and a genetic code In fact enzymes, antibodies, hormones and many other chemical mediators have a proteic structure. Therefore, the synthesis of proteins is essential for the integrity of our organism and to our survival Proteins are a valuable material which our body daily receives through alimentation to substitute and renew those which are damaged daily In a healthy fasting subject, there are usually mechanisms activated in order to save protein metabolism by using fat deposits. the body eats itself up in order to produce the energy necessary to live (cardiac metabolism, pulmonary ventilation) and to maintain the regeneration of some tissues (haemopoiesis, intestinal mucose, skin) Our current knowledge about the physiopathological mechanisms that regulate the metabolic response to injury is not complete and we know even less about the cause Clowes' group isolated a polypetide factor in the plasma of septic patients which was able to produce a release of aminoacids in culture broth from muscular rat tissue *in vitro*. It may be that the proteolytic effect is the stimulation of the PGE_2 synthesis, since the proteolysis does not appear if muscular tissue has been treated with indomethicin.

Advanced gastric cancer: 6 years' experience of 304 operated patients

U. Cosce, V Ingravalieri, I. Caristo, W. Fanichella,
G. Buluggiu, D. Aiello, F. Cangemi and P. Cavaliere
Divisione di Chirurgia Generale, Osp. S. Paulo, Savonese via Genova 17100, Savona, Italy

The frequency of cases of advanced gastric cancer is a problem despite the improvement of preoperative diagnostic techniques. In Italy this pathological finding is responsible for a high morbidity and mortality rate

During the period 1990–1996, 323 patients have been seen at our Surgical Department. 304 had been operated on, with a 94 per cent operation rate. One hundred and sixty-one (32·9 per cent) patients underwent a radical resection surgery (51 total gastrectomy, 110 subtotal gastrectomy with D1-D2 lymphadenectomy) Another 102 patients (33·5 per cent) underwent a palliative resection: 69 palliative gastrectomy with D1 lymphadenectomy and 33 gastroenteric bypass. Explorative operations were performed for the remaining 41 patients (13·4 per cent). Among the 304 patients operated on, 112 presented an advanced gastric cancer, in whom a radical resection was possible in only 37. The survival after the radical surgery was 98 per cent after 6 months and 46 per cent after 5 years. A significant reduction in survival occurs in the advanced cases.

The authors, as with others, point out the difficulty of early diagnosis and the preoperative prediction of resectability. They emphasize the importance of radical surgery with an extended lymphadenectomy for the treatment of gastric cancer.

Malignant hemangiopericytoma

O. Datz and G. Mangold *Department of Surgery, Kreiskrankenhaus, Lahr, Germany*

Hemangiopericytoma is a rare soft-tissue tumour, the histological classification and prognosis of which often proves to be very difficult The biological behaviour of these tumours also seems to vary considerably We report our experience with two patients

A tumour with a diameter of about 13cm in the epigastrium of a 57-year-old female patient proved to be inoperable because of expansive intra-abdominal metastases. In the second case a tumour of about 8cm was removed from the sigmoid mesentery of a 46-year-old female patient. In 1982, the histological diagnosis of extrauterine endometrial sarcoma was made. She was readmitted because of an expansive recurrent tumour in the left hypogastrium and metastases in her liver. Both tumours were removed in two separate operations, including a left hemihepatectomy. The histological and immunohistological examination showed a malignant hemangiopericytoma. When the slide preparations of the earlier operation were compared with those of the second operation, the diagnosis proved to be the same The patient has been without recurrence for 12 months.

Malignant hemangiopericytomas are rare and may have very different biological behaviour and completely different prognosis

Peritonitis treatment in children using abdominal hypothermia

V.B. Davidenko and Y.M. Popenko *Clinic of Infant Surgery, Kharkov, Ukraine*

One of the methods of intensive postoperative therapy in the treatment in children with complex peritonitis is local abdominal hypothermia, used in the Kharkov Clinic of Infant Surgery Hypothermia is performed using a universal hypothermic device, equipped with a control unit that enables regulation of the intensity, speed and duration of cooling. Abdominal hypothermia was used in 87 patients with generalized peritonitis It contributed to early normalization of vital signs, protein and water-electrolyte metabolism amd temperature. There is marked hypothermic analgesic effect as well as stimulating influence on intestinal peristalsis.

We observe more rapid decrease of inflammatory conditions in abdominal cavity and intoxication stage.

Abdominal hypothermia is an effective method for the treatment of peritonitis in children and contributes to patient recovery, reduces complications and shortens intensive therapy stay

The effect of various types of splenectomy on the development of B-16 melanoma in mice

C. Fotiadis, G. Zografos, K Aroni, B Doussaitou, M. Sechas and G. Skalkeas *2nd Propedeutic and 3rd Surgical Department, Athens University, Greece*

Two hundred and sixty CB57BL/J6 mice were used in an experimental protocol designed to investigate the effects of four different varieties of splenectomy on the growth rate of subcutaneously implanted GB-16 melanoma In addition the mean and absolute survival of the mice, the histopathology of the tumour and the effects of the same procedures on the immunological status of the tumour-bearing animals as assessed by serum IgG levels and immunoelectrophoresis were determined. The following were found. (a) splenectomy performed 1 week after B-16 melanoma tumour implantation in mice, i.e. in the early period of oncogenesis, lengthened the survival of the grafted experiments, delayed tumour growth, reduced the 'activity' of the tumour and caused pseudoencapsulation of the tumour by fibrous tissue It increased but not by a statistically significant degree ($P > 0{\cdot}05$) the circulating levels of the IgG immunoglobulin. (b) Splenectomy performed 4 weeks prior to grafting of the same tumour did not affect the circulating IgG levels nor did it prolong survival; however it reduced the rate of tumour growth and pseudoencapsulation of the tumour was observed. (c) Splenectomy at the early stages of oncogenesis in combination with surgical removal of the primary tumour increased absolute and mean survival, delayed the tumour growth rate, increased the time to relapse and reduced the 'activity' of the pseudoencapsulated tumour.

Postsplenectomy portal vein thrombosis in haematological patients

P. Gousis, C. Kitsou, E Mouzakioti, N. Legakis and G. Androulakis *4th Surgical Department, General Hospital of Piraeus, 3 Fanarioton Str. 184 54 Piraeus, University of Athens, Greece*

Portal vein thrombosis (PVT) after splenectomy for haematological disease has been reported with variable frequency

During the last 5 years (January 1991–December 1995) 43 patients with haematological disease underwent splenectomy in our department (age range 15–31 years) Of these patients 38 were thalassaemic, three with idiopathic thrombopenic purpura and two with drepanocytic anaemia We also performed autotransplantation of splenic tissue in 11 of them. All of our patients have been followed up by U/S in any case of unexpected abdominal discomfort or postoperative fever

PVT was diagnosed in five patients (11 6 per cent). Three of them had splenic autotransplantation (27·3 per cent) PVT in our patients presented from 2 days to 1 year after splenectomy and its diagnosis was confirmed by selective digital angiography. The PVT patients did not receive any additional treatment because of alterations of liver function secondary to their haematological disorder

Of the PVT patients four (80 per cent) developed recanalization of the portal vein without complications in a 6-month period, while one (20 per cent) died because of disseminated intravascular coagulation on postoperative day 17

Nutritional support for postoperative gastrointestinal fistulas

P. Grilli, A. Maturo, C. Nwamba, F.M. Fiore, M.T. Proietti and E. De Antoni *III Department of Surgery, University of Rome 'La Sapienza', Viale Regina Elena 324, Rome, Italy*

One of the major complications of digestive surgery are postoperative fistulas The value of parenteral (TPN) and enteral (EN) nutrition for the treatment in postoperative gastrointestinal fistulas is examined

The authors report from 1981 to 1996 on a retrospective study a total of 613 patients treated with TPN and EN, 29 of which had postoperative digestive fistulas.

All patients were evaluated by immunological and multiparameter tests. In 21 patients fistulas closed within a mean time of 23 days of nutritional treatment. This is very important because it avoided a second operation in about 80 per cent of the 29 patients treated When prolonged nutritional treatment of more than 4 weeks does not resolve a fistula, further surgery becomes inevitable.

Nutritional support proves to be a valid therapeutic alternative in the treatment of postoperative gastrointestinal fistulas.

How an ambulatory surgery programme affects the activity of a general surgery service in a community hospital

L.A. Hidalgo, J.M. Badia, M. Prats, J. Feliu, J. Suñol and J M. Gubern *Department of Surgery, Consorci Sanitari de Mataró, Lepant 13, 08301 Mataró, Barcelona, Spain*

The development of an ambulatory surgery programme can optimize the activity of a general surgery service. This applies mainly to the substitution index and sparing of inpatient resources

Aim: To evaluate the impact of a hospital-controlled integrated ambulatory surgery unit (ASU) in the activity of a General Surgery Service in a public 300-bed hospital.

Methods: From June 1994 to December 1995, 470 patients belonging to the general surgery service were operated in the ASU. The overall substitution index and the index for each specific procedure have been evaluated. The economic impact on the Service and the changes in the utilization of the resources have been analysed.

Results: The overall substitution index for general surgery was 27·2 per cent Most frequent procedures were: pilonidal cyst, groin hernia, benign breast tumour, anal fissures and cutaneous or subcutaneous benign tumours. The mean number of operations per month was 26 (16–40). A progressive increment was observed during the study period. General Surgery procedures represented 29·5 per cent of all ASU activity Substitution index for most frequent diagnosis were: pilonidal cyst (71 per cent), groin hernia (23 per cent), benign breast tumour (48 per cent), anal fissures (75 per cent) and cutaneous or subcutaneous benign tumours (98 per cent). The yearly bed surplus in the General Surgery Service due to ASU activity was 4 beds

Conclusions: A good overall substitution index was obtained during the first 18 months of the ASU. For some diagnoses the substitution index reached 70–90 per cent This allowed a better utilization of the inpatient resources in the General Surgery Service with some economic savings

A new collagenous biomaterial for plastic strengthening of gastrointestinal anastomoses

I. Iliev, V. Kavardjikova, K. Kjossev and P. Mitev *Department of General Surgery, Military Medical Academy, Sofia, Bulgaria*

The restoration of the gastrointestinal tract integrity using different kinds of anastomoses still offers unsolved problems. Many operative methods have been tried, but unfortunately the incidence of anastomotic leakage remains high

This report presents experimental investigation of plastic strengthening of gastrointestinal suture lines. A new material, called Recollen, has been used. The morphological changes both of the graft and the intestinal wall have been studied. Sixty dogs underwent: (a) gastrotomy with interrupted single-layer closure (n = 20), (b) partial resection of the left colon with end-to-end single layer anastomosis (n = 40). A sheet of Recollen (width 3cm) was fixed by interrupted sutures around the anastamosis. Laboratory data were collected and planned re-explorations were performed on days 3, 4, 7, 15, 30 and 120. No evidence of leakage, strictures, and adhesions around the graft was noted. Histology confirmed satisfactory vascularization of the graft and good tissue tolerance.

A new method for open management of advanced diffuse peritonitis

I. Iliev, V. Kavardjikova, P. Mitev and K. Kjossev *Department of General Surgery, Military Medical Academy, Sofia, Bulgaria*

The Etappen-lavage combines both the advantages of the 'open abdomen' and the closed peritoneal lavage. The authors present their experimental model of Etappen-lavage using laparostomic set (LS) created by them. It consists of polyester antiadherent mesh sheet containing two self-adherent bands of 'velcroanalog' type. This method allows: daily manual explorations; complete cleansing of the peritoneal cavity; debridement; and aggressive lavage.

The experiments were performed upon 20 dogs. The experimental model of generalized peritonitis (GP) was achieved by incomplete suture of colon (n = 10) and stomach (n = 10). When GP was obvious the LS was inserted followed by daily re-explorations. It was removed after abatement of all septic symptoms on average after 10 to 14 days. Eighteen dogs survived (90 per cent).

The advantages of the Etappen-lavage using the new LS are as follows: much more effective drainage of the peritoneal cavity; early diagnosis of recurrent peritonitis; easy and rapid access for reoperation and drainage when necessary; prevention of tension necrosis and dehiscence of abdominal closure and a reduction of abdominal compartment pressure. The use of the LS was demonstrated as being rapid, simple and safe.

Trophic effects of recombinant human growth hormone (rhGH), zinc and glutamin (GL) on defunctioned small bowel in rats

A. Kartal, A.A. Dilsiz, A. Kaymakçı, S. Duman, M. Aktan and S. Yol *Department of General Surgery, School of Medicine, University of Selçuk, 42080, Akyokuş-Konya, Turkey*

The aim of this study was to investigate the effect of these three nutrients in the rat isolated intestine. The study was performed on defunctioned loop of small bowel in 40 rats. A vascularized proximal jejunal loop, 15cm in length, was prepared and separated from the intestine and its two ends brought out through the abdominal wall as mucous fistulas. Gut continuity was restored by jejunojejunostomy. The rats were divided into four groups, each of 10 animals. All groups had standard nutrition by mouth. In addition to this, the second group had rhGH (0·4mg/kg/day), the third group zinc sulphate (1mg/kg/day) and fourth group L glutamin (0·2g/kg/day). The first group acted as the control. At the end of the third week, all rats were killed. The defunctioned loop and intact jejunum including the anastomosis were resected for histological examination when length of villi and mucin (goblet cells) were measured. In the last three groups, the length of villi and number of goblet cells increased significantly ($P \leqslant 0{\cdot}001$) in defunctioned loops compared with controls. Glutamin had the best trophic effect of the substances on defunctioned loops.

In conclusion, rhGH, zinc and GL have positive trophic effect on defunctioned small bowel villi and goblet cells in rats and can prevent atrophy within an isolated jejunal loop.

The incidence of DVT with and without LMWH prophylaxis in general surgery patients

J. Kutlay, Y. Ozer and M. Dogan *SSK Ankara Hospital, Ankara, Turkey*

In this two-phase study, our first aim was to establish the actual incidence of postoperative deep vein thrombosis (DVT) in general surgery patients in Turkey, and secondly to assess the efficacy of thromboprophylaxis with low molecular weight heparin (LMWH) in a similar patient population.

Two hundred and fifty general surgery patients with moderate and high risk of deep vein thrombosis were investigated by colour Doppler USG, pre- and postoperatively. Ascending venography was done in presence of positive clinical or ultrasonographic evidence of DVT, to confirm the diagnosis. In the first step, the overall incidence of DVT in moderate and high-risk patients without any prohylaxis regimen was found to be 13·5 per cent. One patient (0·4 per cent) had non-fatal pulmonary thromboembolism confirmed by ventilation-perfusion scintigraphy. In the second phase with addition of a LMWH prophylaxis regimen (dalteparin sodium-Fragmin), the DVT incidence reduced to 6 per cent. Correct diagnosis of DVT based on clinical findings alone was less than 40 per cent, suggesting that clinical examination is notoriously unreliable in establishing the diagnosis of postoperative DVT. Sensitivity and specificity of colour Dopper USG in the diagnosis of lower extremity DVT was calculated as 95 per cent and 92 per cent, respectively.

In conclusion, postoperative DVT is an important and preventable complication which may lead to high morbidity and mortality in general surgery patients. Thromboprophylaxis with LMWHs reduces risk of postoperative DVT, LMWH are both cost-effective and efficient alternatives in thromboprophylaxis in general surgery patients.

Computerizing operating rooms: unavoidable challenge?

E. Janicaud, D. Thorin and J.-C. Givel *Service de Chirurgie, 1011 CHUV-Lausanne, Switzerland*

Present developments on public health demand optimal management of resources. In this regard, computer systems play a prime role. In hospitals, the management of large suites of operating rooms generates difficult administrative problems requiring efficient computer support. Planning and managing the flow of patients, employees and equipment as well as financial and quality control calls for the development of specific software. This paper presents characteristics and modalities of introduction of one of these tools.

At our institution, the SIBAGEST software, developed by Rousseau in France, allows the managment of surgical and anaesthetic activities. It also permits the extraction of data for financial and statistic purposes. Implementing such a system requires important cultural changes plus alteration to the structure of resources and materials. The process is long and complex, but it is essential to obtain the active involvement of all system users. The input of computerized data in real-time increases reliability significantly. Training prior to using the system improves efficiency and independence, specially for the operating room staff.

Starting a computerized database system in surgical facilities presents a difficult cultural and functional change. This is mainly due to the diverse mentality of the participants and the constant chance of unexpected occurrences. The benefits of the system are not immediately appreciated by the users who tend to resent it as an additional burden. Later on, the rewards of the initial efforts emerge. The system gradually facilitates tasks and permits better use of resources. It is therefore an unavoidable challenge!

Minimally invasive retroperitoneoscopic sympathectomy: techniques and results of the retroperitoneoscopic approach

M. Jantschulev, H.-D. Czarnetzki, U. Helmke, S. Schulz and P. Schwanitz *Klinikum Sudstadt Rostock, Department of Surgery, Suedring 81, 18059 Rostock, Germany*

Peripheral vascular obliteration of the leg provides an indication for retroperitoneoscopic lumbal sympathectomy. Lumbar sympathectomy is a procedure that aims to dilate the vascular tree to improve peripheral perfusion. In addition it can be used in combination with reconstructive bypass surgery to reduce peripheral resistance for a better postoperative flow. We use a balloon dilatator to create an operating space in the retroperitoneum which is maintained by introducing carbon dioxide with two 5-mm ports we perform the resection of the lumbal sympathic chain from L2 to L4 Much attention must be paid to neighbouring anatomical structures No complications have occurred in 30 patients although conversion to open surgery has been required in two cases because of gas loss into the peritoneum.

Retroperitoneoscopic sympathectomy offers patients the benefits of a minimally invasive surgical technique causing less pain and achieving the desired effect on the peripheral vessels that appears equal to open surgery

The effects of intestinal ischaemia: reperfusion injury on several vascular beds

C. Koksoy*, A Kuzu†, K. Buharalıoğlu‡, S. Uydeş‡, F. Akar‡ and M Kesenci§ *Departments of Surgery, *Ankara Oncology Hospital, †Ankara Numune Hospital, †Department of Pharmacology, Gazi University, Faculty of Pharmacy, §Sevgi Hospital, Ankara, Turkey*

Intestinal ischaemia-reperfusion (IR) injury leads to functional impairments which may contribute to the development of multiple organ failure in several organs and systems as well as the intestines. The aim of this study was to examine the remote organ arteries for endothelial cell function following intestinal IR

Male New Zealand rabbits underwent 1 h of intestinal ischaemia and 2 h reperfusion ($n = 9$) or sham operation ($n = 8$) Then renal, superior mesenteric, carotid, pulmonary arteries and abdominal aorta were removed and placed in an isolated organ bath perfused with oxygenated Krebs' solution. After a phenylephrine dose–response curve was obtained, arterial rings were constricted submaximally with phenylephrine to examine different mechanisms of vascular smooth muscle relaxation by using acetylcholine, sodium nitroprusside and isoproterenol

Maximal vasoconstriction response to phenylephrine in superior mesenteric artery was significantly greater in the IR group than sham group (240 per cent *vs* 150 per cent vasoconstriction, $P < 0{\cdot}05$). But vascular smooth muscle relaxation response to acetylcholine, sodium nitroprusside and isoproterenol was not different between groups.

These data suggest that 1 h of intestinal ischaemia and 2 h of reperfusion does not have an effect on remote organ arteries except for the superior mesenteric artery In this model longer ischaemic or reperfusion periods may lead to vascular endothelial dysfunction

Recurrence after surgical treatment of malignant melanoma: skin graft *vs* primary closure

M M. Konstadoulakis, N Ricaniadis, C Karakoussis, N Apostolodis, A Manouras, M. Leandros, B. Pararas and B Golematis *1st Department of Surgery, Laboratory of Immunology, Hippokration Hospital, Athens Medical School, Athens, Greece*

A retrospective study was carried out on 919 patients who underwent surgical treatment of a malignant melanoma. Males accounted for approximately 50 per cent ($n = 457$) The median age was about 50 years. The majority of the patients had wide excisions of their primary tumours ($n = 866$, 94 per cent), 211 had lymph node dissections (23 per cent) and eight had amputations (<1 per cent) We used a multivariate analysis to determine the effect of variables (sex, ulceration, age, thickness, site and stage) on the dependent outcomes (local recurrences, distant and regional recurrences) There were 611 patients that had primary repair, and compared with 308 patients that required skin grafting for the defect after resection of the melanoma Of these, there were 710 patients with Stage II malignant melanoma treated in RPCI rate It was found that repair method was related to the Roswell Park Cancer Institute ($P = 0{\cdot}01$) This may be due to the way the excision is performed when using a primary closure. We resected greater longitudinal margins, with more lymphatics increasing the chance of complete eradication of the malignant melanoma cells Our results suggest that skin grafting may increase the chance of recurrent disease. Further studies are needed to define the risk of recurrence following skin graft repair to a malignant melanoma resection site.

Subcutaneous naphtha injection: a review of 48 cases

P. Krastanov, K. Kjossev, J. Losanoff, I. Iliev, P. Mitev and V Mutaftchijski *Department of General Surgery, Military Medical Academy, Sofia, Bulgaria*

There are several single case reports describing effects of subcutaneous petroleum distillate injection Such injections constitute a small but important group of accidental poisonings, suicide attempts or attempted murder and require greater awareness of systemic complications as well as immediate extensive surgical debridement followed by plastic reconstruction of the affected area.

Between 1986 and 1996, 48 patients were treated in our department because of subcutaneous petroleum distillate (naphtha) injection in an attempt to escape justice All 48 were males, aged between 18 to 24 years (mean age 19·5 years) These cases were classified into three groups according to the site of injection and the size of affected area Three serious complications were observed: one severe pneumonitis developing following admission. A second presented with CNS toxicity after subcutaneous injection of approximately 3 ml naphtha The third patient underwent a below-knee amputation for gangrene

Compartment pressures measured in 19 cases confirmed a compartment syndrome All the patients underwent extensive surgical debridement at the injection site. Cellulitis and sterile abscess formation were found in 64·5 per cent ($n = 31$) and myonecrosis in 35·5 per cent ($n = 17$). Plastic reconstruction was needed in 32 instances

In conclusion subcutaneous naphtha injection is a rare clinical entity. Prompt recognition and adequate aggressive treatment are necessary to prevent permanent disability.

Peritoneal adhesions prevention in the rabbit by sodium carboxymethylcellulose solution (SCMC)

A. Macheras, D. Mandrekas, T. Liakakos, C Fotiadis, N Kakaviatos, A. Lazaris and M. Sechas *Laboratory of Medical Research 'N Christeas', and 3rd Surgical Department of Athens University, Athens, Greece*

Aim: To evaluate sodium carboxymethylcellulose solution 1 per cent (SCMC) to prevent postoperative adhesions compared to normal saline.

Method: Sixty adult rabbits (12 males and 48 non-pregnant females) were divided in three groups (20 animals in each). In the first group the peritoneal cavity was irrigated with normal saline 0·9 per cent In the second group SCMC was instilled into the peritoneal cavity. In the third group (control group) the peritoneal cavity was not irrigated by any material. Three weeks later all the rabbits underwent a second operation through a separate incision and the adhesions were identified, counted and graded according to Nair *et al* scale.

Results: Sixteen (80 per cent) rabbits of the control group and 13 (65 per cent) of the N/S group had significant adhesions. Five (25 per cent) rabbits of the SCMC group had significant adhesions but eight (40 per cent) had no adhesions at all. The postoperative adhesions in the SCMC group were statistically significant less ($P < 0\ 001$) than in the control as well as in the N/S group.

Conclusions: The instillation of SCMC 1 per cent in the peritoneal cavity of rabbits is safe, non-toxic and effective in reducing the incidence and degree of postoperative intraperitoneal adhesions

The dynamics of adaptation reactions in children with acute processes in the abdominal cavity

V.Z. Moskalenko and S.V. Vesely *Department of Paediatric Surgery, Donetsk Medical University, 340003, Prospect ilitcha, 16 Donetsk, Ukraine*

The purpose of our work was the study of clinical reflection of a general adaptive syndrome developing in children with acute surgical pathology of the stomach We investigated 305 children aged from 4 months to 15 years; 208 of them had acute appendicitis including 64 patients with complicated peritonitis. Twelve children had had cryptogenic peritonitis, 52 ileus, 27 abdominal trauma and six girls had acute gynaecological pathology. We studied the changes in peroxide oxidation of lipids and antioxidizing systems and also some other biochemical inductors of stress in all patients. One hundred and twenty biopsies of parietal peritoneum were taken. Immunological parameters were obtained for all children Adaptation reactions have a nosological configuration in the first stages of development of the pathological process dependent upon the aetiological factor It is expressed with different symptoms for appendicitis (peritonitis), occlusive ileus and trauma of stomach. The clinical observations have been confirmed with laboratory investigations. In contrast, evolution of the diffuse pathological process for patients with complicated abdominal processes (progressive peritonitis, early bowel strangulation and leaking anastomosis) do not have nosological configurations independent of the initial cause of the disease The products of peroxidation in these patients were increased. The morphological changes of the pariental peritoneum were changes in the microcirculation and increased pyogenic and necrotic processes. Suppression of immunological reaction occurs in the critically ill. Both local and general non-specific adaptive reactions occur in children with acute abdominal pathology. Clinical manifestations depend upon a combination of aetiological factors, site, magnitude and duration of effects and also individual reactions to organisms.

Retroperitoneal paraganglioma in the Zuckerkandl organ

I. Prieto Nieto, J.P. Perez Robledo, D. Hardisson,
J.L. Palenzuela, R. Corripio and
A. Granado de la Fuente *Hospital 'La Paz', Madrid, Spain*

Introduction: Paragangliomas are tumours derived from neural crest cells that emigrate to the suprarenal medulla and to different levels of the autonomic nervous system. They are usually of retroperitoneal localization and within this region are most commonly found in the para-aortic zone between the origin of the inferior mesenteric artery and the bifurcation of the aorta (30 per cent) We present a clinical case of a patient with paraganglioma in the Zuckerkandl organ which should be taken into consideration in the differential diagnosis of abdominal masses, especially when these are located near to the aorta.

Clinical case: A 37-year-old woman attended the Emergency Department with a periumbilical tumour of 3 months' duration and pain extending over the left lumbar region. Physical examination revealed a periumbilical abdominal mass, that was mobile and slightly painful on palpation On abdominal echography, a rounded 4 × 3cm solid mass was observed approximately 1cm from the bifurcation of the aorta, heterechoic and highly vascularized. In abdominal computerized axial tomography the density of the mass corresponded to soft tissue that was separated from the aorta by a cleavage plane. After injection of contrast medium the tumour had a heterogenous capture with central hypodense zones compatible with necrosis. The area surrounding the mass was highly vascularized but no adenopathies were observed. Intravenous urography revealed both kidneys to be functioning well with external deviation of the left ureter without signs of compression. After diagnosis of a retroperitoneal mass it was treated surgically A middle laparotomy was performed and a highly vascularized oval solid tumour 8 × 10cm was observed above the aorta and the left iliac artery that included the inferior mesenteric artery, sigmoid arteries and the left ureter. The tumour was extirpated after detaching the ureter and the inferior mesenteric artery. The anatomopathological result was paraganglioma. Postoperative progress was favourable. At 6-month follow-up the patient is without recurrence.

Surgical treatment of short intestine syndrome with extensive resections

Y.M. Popenko, V.B. Davidenko and V.A. Zaika *Clinic of Infant Surgery, Kharkov, Ukraine*

One of the most complicated problems in infant surgery is treating short intestine syndrome developed after extensive resections of small intestine. Removing more than a half of the small intestine results in pathological syndrome connected with disorders of intestinal metabolism and absorption that may cause severe homeostatic disorders and progressive cachexia.

Therefore we have experimented with a method of surgical treatment for short intestine syndome. To inhibit the passage of intestinal contents intramural nervous conduction is interrupted in the wall of the small intestine by creating multiple defect of longitudinal muscle layers.

In the last 15 years 103 resections of small intestine have been performed. There have been 11 (10·9 per cent) extensive resections in which the patients have developed small intestine syndrome of different extents. Five of these children were operated on because of ineffective conservative therapy

Our clinical researches suggest that to correct the short intestine syndrome in children our method of surgical treatment may be of benefit.

Development of an integrated major ambulatory surgery programme in a community hospital

M. Prats, L.A. Hidalgo, J.M. Badia, A. Heredia, A. Bianchi, J. Barja and J.M. Gubern *Department of Surgery, Consorci Sanitari de Mataró, Lepant 13, 08301 Mataró, Barcelona, Spain*

The spectacular growth of ambulatory surgery in the 1990s can hardly go unnoticed. All ambulatory surgery units should be continuously evaluated for their results and quality standards.

Aim: To evaluate the outcome of a hospital-controlled integrated major ambulatory surgery unit in a public 300-bed hospital.

Methods: Data required for the study were prospectively collected for all patients operated in the unit. A patient satisfaction survey was done by telephone at 24h and a prepaid mail questionnaire at 2 weeks after the operation.

Results: From June 1994 to December 1995, 1592 patients were operated on in the unit During the same period of time a total of 6298 procedures requiring hospital admission were performed. The surgical specialties and the number of procedures performed were as follows: general surgery (470), orthopaedics (470), vascular surgery (142), ophthalmology (218), plastic surgery (95), gynaecology (54), endoscopy (4) and urology (79). The anaesthetic techniques employed were general anaesthesia (19 per cent), spinal (22 per cent), epidural (1 per cent), nerve block (6 per cent), retrobulbar (12 per cent) and local infiltration (32 per cent) A total substitution index of 25 per cent was achieved Most common procedures were: pilonidal cysts and abdominal wall hernias in general surgery, removal of prosthetic material and carpal tunnel syndrome in orthopaedics, treatment of varicose veins in vascular surgery and cataracts in ophthalmology. Forty patients (3 per cent) had to be admitted on the day of the operation. In 5 per cent of cases the patient made a postoperative emergency telephone consultation. In the early patient satisfaction survey, outcome at 24h was considered good in 836 cases (86 per cent). Moderate pain was the main claim of patients in the questionnaires received (21 per cent).

Conclusions: From the beginning of the programme our rate of hospital admissions was low and patient satisfaction excellent. During the first 18 months a worthy substitution index was achieved. Ambulatory surgery can be successfully implemented in a community hospital.

Results of a 2-year period experience of a one-day surgery programme in our hospital

F. Guspí Sáiz, A Sánchez Marin, J. Doménech,
J. Sánchez Pérez, J.J Sánchez Cano, J.B. Comes, J.M. Jardí
and D. Del Castillo Déjardin *Department of Surgery, Hospital Universitari de Sant Joan de Reus, Universitat Rovira i Virgili, Spain*

Aim: In June 1994 our hospital began a 1-day surgery programme with the aim to reduce the waiting list of our General Surgery Department, preserving the safety and quality required for surgical procedures, and patient satisfaction.
Patients and methods: From June 1994 to May 1996, 383 patients were operated on in our 1-day surgery programme (227 males and 156 females), the mean age was 43·6 years old (range 3–83) All the patients underwent specific inclusion criteria before their admission in this programme The main diagnoses were· groin hernia (169), varicose veins (99), pylonidal sinus (40), incisional hernia (11), and fistula (11), haemorrhoids (16), fistula in ano (10), miscellaneous (27) The main anaesthetic techniques were epidural and spinal
Results: The mean operative time was less than 60 minutes The procedures were performed by a staff member in 185 cases and by a trained resident under staff supervision in 198 cases Three hundred and fifty-three patients (92·2 per cent) left the hospital the same day as the surgical procedure, 44 patients (11·5 per cent) presented with some perioperative complication, and 30 patients (7 8 per cent) had to remain in the hospital Eight patients (2·1 per cent) visited at the emergency room after their discharge Only one patient needed readmission The satisfaction of the patients who entered in this programme reached 98 per cent The waiting time for surgery has decreased from a mean of 18 months to a mean of 10 weeks
Conclusions: The 1-day surgery programme in our hospital has produced an important decrease of the time waiting for the surgical intervention in our hospital To carry out a 1-day surgery programme quality, technical equipment and safety must be as good as shown in conventional hospital setting

Definite surgical treatment of complicated recurrent pilonidal disease with a modified fasciocutaneous VY-advancement flap

T. Schoeller, G. Wechselberger and C. Papp *University Hospital of Plastic and Reconstructive Surgery, University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria*

Different methods for managing pilonidal disease have been described in the literature Recurrence impairs the success of all forms of therapy, but the lowest rates have been reported for reconstructions involving local flaps. Nevertheless treatment of pilonidal disease with a fasciocutaneous VY-flap is not a well established procedure We have modified the surgical technique and use it selectively for complicated recurrent cases. This new surgical technique is described, our experience with this method is analysed and its validity evaluated
Methods: Twenty-four patients with recurrent pilonidal sinus undergoing radical excision and reconstruction with our modified fasciocutaneous VY-advancement flap between 1986 and 1993 were studied retrospectively
Results: Except for two minor transient wound dehiscences in all cases primary healing was achieved. Patients were followed up for a mean of 4·5 years An excellent functional result with acceptable scar pattern was obtained in all 24 patients There was no evidence of recurrence nor impairment of activity
Conclusion: Treatment of complicated recurrent pilonidal sinus with the described technique offers a safe but demanding method for definite reconstruction

The effect of short-term treatment of octreotide on organ histology in experimentally induced acute pancreatitis

A Soran, M. Cete, A. Polat, I. Kuzu, C. Çol and
S. Hengirmen *General Surgery, Ankara Numune Hospital, Opera, Ankara, Turkey*

It is known that long-term therapy with octreotide alters the histology of intra-abdominal organs Our aim was to evaluate the histological effects of short-term administration of octreotide on intra-abdominal organs with experimentally induced pancreatitis by ligating the pancreatic duct. A control operation was performed on Group 1 (n = 10) and Group 2 (n = 10) rabbits. Acute pancreatitis was induced in Group 3 (n = 10) and Group 4 (n = 10). Octreotide was administered subcutaneously for 7 days, 10 mcg/kg/day to Groups 2 and 4 At the end of day 7 blood was drawn and the rabbits were killed and tissue samples were examined

There were no histological changes in gastric, duodenal, gallbladder, jejunum and colon tissue on short-term administration Pancreatic tissue damage was not affected by the administration of octreotide in the pancreatic group, but vascular dilatation occurred in Group 2 Bile duct proliferation, bile duct epithelial proliferation, periportal inflammation and venous stasis increased and hepatocyte atrophy was seen

Current-state splenectomy in chronic lymphoproliferative disorders

*L. Toppi, *L. Corbellini, †E. Orsi and †R. Vellucci
**III Surgical Clinic, University of Rome 'La Sapienza', †General Surgery, University 'G. D'Annunzio', Chieti, Italy*

Splenectomy in chronic lymphoproliferative disorders (CLD) has been a matter of debate for many years Its current state indications are as follows: chronic lymphocytic leukaemia (CLL) and its derivations (prolymphocytic leukaemia, Richter syndrome), hairy cell leukaemia (HCL) and splenic lymphoma with villous lymphocytes (SLVL). Splenectomy associated with chemo- and radiotherapy is the treatment of choice in these pathologies, especially if hypersplenism with severe thrombocytopenia occurs at the same time In SLVL, splenectomy itself prove as curative, involving lasting clinical recovery Specific indications for performing splenectomy were given in the following cases splenomegalies if there was no or low response to chemo- and radiotherapy, large splenomegalies with hypersplenism, splenomegalies with autoimmune haemolytic anaemia, steroid non-responsive, associated with splenic sequestration.

From January 1992 to December 1995 92 splenectomies were performed for various haematological illnesses; 42 patients for CLD (45·6 per cent), 27 females and 18 males (range 41–73 years, mean age 58 years) Operatory mortality was zero. Complications occurred as follows· three pleural sierositis (one of them with left-side subdiaphragmatic abscess, treated by US drainage); two cases of haemoperitoneum (one female being under anticoagulant treatment with calciparine for fibrillating cardiopathy and one male with a severe bleeding disorder, both treated by laparatomy); one pulmonary embolism at Day 7 (medical resolution), one intestinal pseudo-occlusion (repeated laparatomy)

Our results show 23 complete haematological responses, one recurrence and two lethal outcomes (at 13 and 16 months, respectively). All the patients were seen to regain immediately good blood values, more or less for long-standing periods, including a positive resolution of 'occupation' syndrome.

One-day surgery in patient with haematological disease: a procedure for early diagnosis

*R. Vellucci, *E. Orsi, *L. Toppi, †L. Corbellini and
*F.M. Di Matteo **Istituto di III Clinica Chirurgica, Università degli Studi 'G. D'Annunzio', Chieti, †Università degli Studi di Roma 'La Sapienza', Italy*

Early involvement of mediastinal or abdominal lymph nodes by some systemic lymphomas are often observed Surgical procedure (skin-deep lymph node total biopsy) are requested by haematologists for a histopathological diagnosis that allows early haematological treatment.

For many years our team has been working as a Special Service, made up of haematologists, surgeons, anaesthetists, nurses, radiologists for US and CT scan, pathologists, with a dedicated surgery room at our disposal. This day-surgery organization has reached its goal by the early detection of haematological disease with the help of quick and low economical cost procedures, as well as of minimally invasive surgery, finally allowing the patients to return home on the same day, without an overnight stay.

Between January 1989 and December 1995, 2126 patients were operated on in day-surgery management. To minimize the risks, an appropriate patient evaluation was performed: 583 operations were carried out in the axillary, 825 in the neck and 163 in groin region. Of our patients, 563 were over 65 years old In 729 patients (186 patients were over 65 years old) a diagnosis of non-Hodgkin lymphoma was made and 308 patients were affected by Hodgkin lymphoma (44 patients were over 65 years old). In 124 patients, pathological specimens proved to be pulmonary, mammary, thyroid cancers and lymphonodal metastasis

Further operations on other pathologies such as lateral neck and thyroglossal cysts, lymphangiomas, schwannomas, soft-tissue tumours, carotid body tumours, tubercular and aspecific lymphadenyitis, epidermoidal cysts, lipomas, metastatic lymphonodal melanomas and crural hernias were performed as well

Hypocaloric parenteral nutrition and protein metabolism in the immediate post-surgical period: a mass spectrometry study

M. Vidal, J.A. Baena, E. Gemar, J. López-Hellín,
E. García Arumí, T. Fernández Cuadrado and C. Ruiz
Servicios de Cirugia General y de Investigaciones Metabólicas Santiago Grisolía, Hospital Universitari Vall d'Hebron, Barcelona, Spain

Aim: To determine if hypocaloric parenteral nutrition (HPN) is better than standard glucosaline support (GS) in portsurgical patients.
Design: A prospective study, randomized, double blind for 1 year.
Patients: Eighteen patients, age range 30–80 years, with good nutritional status, undergoing elective abdominal surgery involving 5 days' starvation.
Interventions: Patients were randomized into two groups immediately after surgery both groups received GS (day 0), followed by 5 days with GS (28 kJ/kg/day) or with HPN (28 kJ/kg/day + 1 g AA/kg/day). Protein synthesis and breakdown were determined at day 0 and 5 by using a continuous infusion of [^{15}N]glycine and measuring ^{15}N in urinary urea with an isotope ratio mass spectrometer.
Results: NPH group reduced synthesis and breakdown day 5 *vs* day 0 ($P <$ 0·0001 and $P <$ 0·0005 respectively), showing normal values for synthesis and breakdown. GS group showed synthesis and breakdown higher than normal ($P < 9 . 10^{-6}$ and $P < 4\ 10^{-5}$ respectively), with an increase day 5 *vs* day 0 ($P <$ 0·02 and $P <$ 0·03 respectively).
Conclusions: These results show that HPN offers better nutritional support in postsurgical patients than GS HPN achieves a normalization of the protein metabolism after 5 days. The amino acid supply of HPN is essential to stabilize protein metabolism, severely disrupted by surgical stress.

Surgical therapy of malignant tumours of the retroperitoneum

K. Wendl and A. Richter *Chirurgische Klinik, Klinikum der Stadt Mannheim, Theodor-Kutzer-Ufer 68167 Mannheim, Germany*

Malignant tumours of the retroperitoneum are rare, constituting only 0·3 per cent of all operated malignancies.

Seventy-three patients underwent surgery between 1 January 1976 and 31 December 1995 for malignant retroperitonal tumours. The median age was 55·9 years, highest incidence was observed in the 51–60-year-old patients. Male to female ratio 1·21.1. In 64 per cent (*n* = 47) R0 resection was achieved, in 38 per cent (*n* = 28) additional resection of adjacent organs was needed in 8 per cent (*n* = 6) vessel resection with vascular grafting was necessary In 23 per cent (*n* = 17) the operation was terminated as an exploratory laparotomy, in 12 per cent (*n* = 9) only a reduction of tumour size was possible We found the following histological types· liposarcoma (*n* = 23), leiomyosarcoma (*n* = 18), malignant Schwannoma (*n* = 7), non-Hodgkin lymphoma (*n* = 5), malignant fibrous histiocytoma (*n* = 3), fibrosarcoma (*n* = 3), neurofibrosarcoma (*n* = 2), malignant teratoma (*n* = 1) and non-classified tumours (*n* = 11).

Follow-up of patients is available for between 5 months and 12 years The 5-year survival rate following R0 resection was 38·5 per cent, none of the other patients survived longer than 23 months. These unsatisfactory long-term results of retroperitoneal tumours are mainly due to late manifestation and large tumour size (maximum tumour weight 10 kg in our patients) resulting in non-resectability.

The effect of haloperidol on serum lipid levels and experimental atherogenesis

G.N. Zografos, P. Karayannakos, D. Perrea, I. Donta,
C. Fotiadis, G. Papastratis, N. Kakaviatos, J. Gogas and
M Sechas *Laboratory of Experimental Surgery and Surgical Research, University of Athens, Greece*

The aim of this experimental study was to investigate the effect of haloperidol on the development and extent of atherosclerotic plaques

Rabbits in the first series (A) were fed normal diet while animals in the second series (B) were fed a diet of 2 per cent cholesterol and 6 per cent corn-oil, for 6 weeks. The first group of each series received normal saline daily and the second received haloperidol 0·4 mg/kg × 3 daily per os. The animals were killed after 6 weeks. Haloperidol did not reduce their body weight and the serum levels of total cholesterol, total lipids, triglycerides or HDL-cholesterol. The aortas were removed from the aortic arch to the iliac bifurcation and mapped by the polar coordinate method No atherosclerotic lesions were observed in animals of series A. There was a significant difference in the extent of atherosclerotic lesions between animals of series B which received haloperidol and animals of series B which received normal saline The exact mechanism of this reduction of atherosclerotic lesions is not clear.

Operative wound seeding of tumour cells

A.J. Curran, D. Smyth, M. Toner and C. Timon *Department of Otolaryngology/Head and Neck Surgery, St. James's Hospital, Dublin, Ireland*

Carcinoma of the upper aero-digestive tract is a common disease of western society and local recurrence after conceivably curative resection a major problem. Cells exfoliated from malignant tumours have been considered capable of implanting and giving rise to local recurrence Recent literature has suggested that this can be reduced by measures taken intra-operatively such as changing gloves and instruments No prospective study has examined possible contamination from gloves and instruments used during surgery

This prospective study examined washings from 15 patients undergoing head and neck surgery. Following removal of the main tumour specimen all surgeons washed their hands in a solution containing a cell fixative All instruments were washed in a separate container Samples were spun in a centrifuge and the supernatant fluid aspirated. The deposits were stained using the PAP technique

Nine of the fifteen specimens contained exfoliated malignant cells in both glove and instrument washings. From this study it is clearly important to change gloves and instruments prior to irrigation of the operative field with a tumoricidal agent and prior to any subsequent reconstruction

Neck management in malignant parotid tumours

F. Ionna, P. Delrio, L. Pezzullo and V. Formisano *Division of Surgical Oncology B, National Cancer Institute, Via M. Semmola, Naples, Italy*

Surgery is the treatment of choice for parotid neoplasms. Radical neck dissection is best reserved for those patients with malignant tumours who present with clinical evidence of nodal metastases Review of the experience accumulated in our Division during the last 20 years indicates that lymph-node involvement occurs in about 18 per cent of patients with parotid gland carcinomas, most of whom have obvious metastases on admission. Occasionally, elective lymphoadenectomy may be appropriate to facilitate resection of large tumours which extend into the neck. It may also be indicated in selected patients with anaplastic, squamous or high-grade mucoepidermoid carcinomas, who are at particularly high risk of occult nodal involvement. Currently, there is growing interest in a limited staging lymphoadenectomy, usually a sapraomohyoid neck dissection, in this setting.

When cervical metastases are palpable, however, modified neck dissection would seem ill-advised considering the poor prognosis observed in these patients. We reported 10-year disease-free survivals ranged from 95 per cent to 77 per cent to 17 per cent in patients with Stage I, Stage II and Stage III tumours, respectively.

Survival curves based on histological type alone show a trend towards better results in patients with acinic cell carcinoma and a less favourable outcome in those with adenocarcinoma, squamous carcinoma and adenoidcystic carcinoma but the differences are not statistically different

Incidence of facial fractures according to site, treatment and type of anaesthesia. A 9-year survey (1986–95)

K. Marti, C. Martis, E. Vairaktaris, N. Papadogeorgakis, I. Iatrou and G. Zografos *Maxillofacial Surgery Clinic, Evangelismos Hospital, University of Athens, Greece*

From 1 January 1986 to 31 December 1995 2443 cases of maxillofacial fractures were treated in our Clinic Of these 1703 patients were admitted to the Hospital and treated surgically for fractures of the mandible, middle third of the face, nasal bones, zygomatic complex and orbital regions. The remaining 740 were also treated surgically for similar fractures, and followed up as well, in the outpatient department.

It is important that although the majority of patients were operated on under general anaesthesia, a large number (45 per cent) were treated surgically under local anaesthesia with or without sedation. This is consistent with the worldwide trend to the greater use of local anaesthesia, due to the high incidence of complications related to general anaesthesia

All surgical methods used for treatment of facial fractures are related to the fracture location, the mandible fractures being treated by open reduction and the use of plates and/or intramedullary fixation, the fractures of the middle face or zygomatic bone with open or closed reduction and the naso-orbital region by combination of methods with or without the use of various grafts.

Reconstructive microsurgery in inferior laryngeal nerve injuries: today's report

A. Ortensi, V. Marchese, A. Lentini and F. Stocco *Servizio di Microchirurgia, Istituto di III Clinica Chirurgica and Università di Roma 'La Sapienza', Rome, Italy*

Inferior laryngeal nerve (ILN) first described by Galen of Pergamus in 200 BC, has been attentively studied over the years especially for its functions of laryngeal motility, phonation and breathing

Various authors have concentrated their attention on the ILN especially in relation to complication following thyroid surgery. the identification, the dissection and the preservation of the nerve is the crucial part of the operations on thyroid gland and neck in general. Today the ILN may be repaired using reconstructive microsurgical techniques It is important to follow a logical sequence of steps in approaching the problem of ILN injury: end-to-end neuroraphy (fascicular or using a graft) has to be performed. Wherever possible repair should be attempted during the same operation when the lesion is identified, or as soon as possible thereafter An alternative operation, recognized as giving better function by many authors, is the anastamosis of ILN and the hypoglossal loop In particular the terminal branch of the hypoglossal loop that supplies the sternothyroid muscle is ideal because of its proximity to the injured stump of the ILM Seven cases have been treated in the last 2 years Five cases have restored their phonation; (c) besides the operation described, palliative prodcedures are still valid i e the injection of Teflon into the paralysed vocal cord, type I thyreoplasty (Isshiki) or alternative thyreoplasty as performed by the otholaryngologists

A three-part Le Fort I osteotomy combined with a bilateral sagittal splitting, augmentation and implantation

W. Schlossarek *Sanatorium Hera Department for Oro- and Maxillofacial Surgery, Löblichgasse 10, 1090 Vienna, Austria*

The 21-year-old female patient suffered from a severe hypoplasia of the midface and a midline shift of the maxilla combined with a progenia with atrophic alveolar ridges on both sides. In a one-stage procedure she underwent a three-part Le Fort I osteotomy to move the maxilla forward, bilateral sagittal splitting of the mandible combined with a chin osteotomy, and augmentation of the edentolous parts of the mandible with bony transplants from the iliac crest and insertion of 8 IMZ implants All osteotomies were stabilized by miniplates and miniscrews, 4 months after the operation the implants were retrieved and replaced by screw-fixated porcelain crowns and bridges.

Studies on intraoperative protection of recurrent laryngeal nerves during thyroid surgery

G. Strózyk*, J.M. Narębski*, L. Pomorski*, K. Kuzdak*, J. Brzeziński*, J. Tazbir*, S. Wieczorkowski†, R. Wichman* and K. Kołomecki* **Clinic of Endocrinological Surgery, Medical University of Lodz, †Technical University of Lodz, Poland*

Aim: We would like to present results of our studies on development of the method enabling us to monitor the anatomical and functional condition of recurrent laryngeal nerves and therefore voice during partial and total thyroidectomy. We have obtained permission from the Ethical Commission for Experiments on Animals to conduct these studies.
Methods: The study group consisted of 60 animals. A balloon connected to a gas container is placed between the vocal cords. Pressure changes within the balloon register short involuntary contractions of the vocal cords caused by pressure or electrical stimulation of the recurrent laryngeal nerve area.
Results: The experimental stage involving thyroid surgery was performed on two groups of experimental animals. In all animals from the monitored group, recurrent laryngeal nerves were precisely located without difficulty. For those without monitoring of vocal cords paralysis, complications varied from 1·5 per cent to 16·5 per cent depending on the thyroid surgery performed. Despite many reports about the protection of the recurrent laryngeal nerves, no method seems to be effective enough to be routinely used during partial and total thyroidectomy
Conclusions: The introduction of the vocal cords monitoring system allows precise intraoperative localization of the recurrent nerves

Experience and complications of thyroidectomy

H. Yavuz, A.R. Tumer, F.M. Avsar, M. Doganay and N.A. Kama *Ankara Numune Hospital, 4th Department of Surgery, Ankara, Turkey*

Introduction: Technical improvements in thyroid surgery have decreased the rate of complications to 5–15 per cent. This rate reflects the experience of the surgeon. In this study, the relation between surgical experience and complications has been reviewed
Materials and methods: Two hundred and sixty-two patients underwent thyroidectomy between 1 October 1991 and 31 December 1994. All of the patients are being followed using a specially designed proforma in our clinic.
Results: Thirty-eight of the patients were males, 224 were females, and their ages ranged between 13 and 80 years. Two hundred and twenty-eight patients (87 per cent) were operated on for multinodular goitre, 14 (5·3 per cent) for thyroid malignancy, 14 (53 per cent) for recurrent goitre, five (1·9 per cent) for toxic diffuse goitre, and one (0·4 per cent) for thyroiditis. Bilateral subtotal thyroidectomy was performed on 202 (77·1 per cent) patients, unilateral subtotal thyroidectomy on 34 (13 per cent), total thyroidectomy unilaterally plus subtotal thyroidectomy on the other lobe on 18 (6·8 per cent), total thyroidectomy on four (1·5 per cent), and radical neck dissection on four (1·5 per cent). Eighty-nine (34 per cent) of these operations were performed by a specialist, 132 of them by a senior assistant with the help of a specialist and 41 (16 per cent) by senior assistants. Transient inferior or superior laryngeal nerve dysfunction developed in 34 (15 per cent) patients, transient hypoparathyroidism in six (2·3 per cent), hypothyroidism in three (1·1 per cent), haematoma and echimosis in seven (2·7 per cent), seroma in five (1·9 per cent) and infection in five (1·9 per cent) patients When total complication rates were compared to the experience of surgical team, complications arose in 35 per cent of the cases performed by a specialist, in 13·5 per cent of cases performed by a senior assistant with the help of a specialist and in 36·6 per cent by senior assistants alone ($P = 0{\cdot}098$).
Conclusions: The data of this study show that the thyroidectomy performed as part of a surgical education programme could be confidently performed by senior assistants with the help of a specialist surgeon.

Hernia

Giant morgagni hernia (with mobile right colon and ileus in right hemithorax) in an adult

C. Avgoustou, M. Constantinou and J. Zormbas *2nd Department of Thoracic Surgery, District General Hospital of Chest Diseases 'Sotiria', Athens, Greece*

A case of a giant morgagni hernia is described in a woman aged 65 years, which was occupying the lower third of the right hemithorax and which was successfully repaired.

The patient was complaining of cough, dyspnoea, constipation and recently worsening non-specific 'dyspeptic' symptoms A suspicion of the presence of intestine in right hemithorax was made from routine chest films Further diagnostic evaluation consisted of CT scan and gastrointestinal imaging with contrast media. Tests of ventilatory capacity showed a restrictive pattern (FEV_1 = 760/1620 or 46·8 per cent, FVC = 880/1970 or 44 5 per cent). Operative repair was performed through an abdominal incision and consisted of reduction of the hernia contents (mobile right colon with vermiform appendix, ileum, greater omentum) and resection of the true hernia sac as well The large diaphramatic defect was closed, with colopexy of the right colon

Because of preoperative respiratory disease and an unexpected mild pulmonary embolism on the second postoperative day low molecular weight heparin was given, mechanical ventilation was required for a period. The patient survived and is now doing well with improved ventilatory volumes (FEV_1 = 1920, FVC = 2360)

Although morgagni hernias are rare and often asymptomatic, they may present with symptoms even in adults. Obesity and increased intra-abdominal pressure may play a role. Elective surgical repair is indicated in most instances to prevent complications. Repair of the defect by a transabdominal approach is preferable.

Two cases of Spiegelian hernia

C. Antunes, F. Manso and A. Capelo *Hospital São Marcos, Braga, Portugal*

Introduction: Spiegelian hernias, or hernias of the semilunar line, are quite rare. According to Spangen, only 815 such hernias were reported before 1985, and subsequently only a very small number of reports appear in the literature. They are more common in females. In 20–22 per cent of the cases they are irreducible Ultrasound assessment may be helpful for diagnosis. We recently had two cases of Spiegelian hernia in female patients. One of the patients was operated on as an emergency due to hernian incarceration on the left-hand side (Richter hernia). The other patient was operated routinely, suffering from hernia on the right-hand side In both cases it was not possible to reach the diagnosis before operation.

Discussion: Spiegelian hernias in females are usually smaller than 2 cm. Age, obesity and increase of intra-abdominal pressure are associated with their development The most useful diagnostic tool is abdominal ultrasound scan. The treatment usually consists on resection of the sac followed by closure of the defect and then closure of the external oblique aponeurosis.

Conclusions: These are rare hernias, more common in old, obese and female patients. The best diagnostic procedure is ultrasound. Closure of the sac and of the hernial defect is sufficient for treatment They rarely recur.

Totally extraperitoneal (TEP) repair of inguinal hernia: 223 cases with a median of 18 months follow-up

M. Berberoğlu, M.M. Ozmen, O.N. Dilek, H.M. Cete, O. Koçak and M. Özer *ITEM Advanced Medical Technologies Education and Training Centre; 1st Surgical Department, Numune Hospital, Ankara, Department of Surgery, University of 100. yıl, Van; Sinop and Ünye State Hospitals, Turkey*

Although it has not been widely accepted due to concerns about efficacy and cost, laparoscopic hernia repair could be an attractive alternative to conventional inguinal hernia repair

Between October 1993 and May 1996, 223 TEP hernia repairs were performed on 213 patients whose age averaged 40 (range 18–76) years. Ninety-five hernias were direct (43 per cent), 118 were indirect (53 per cent), 10 were femoral (4 per cent), 10 were bilateral and eight were recurrent hernias The technique was similar in all patients The median (range) operation time was 45 (20–150) min With the median (range) follow-up period of 18 (3–33) months, only three (1·3 per cent) hernias have recurred and all were due to technical errors which were all recognized within 3 months of surgery. Postoperative complications were seen in 16 patients (7 per cent) including scrotal seroma in seven, haematoma in three, trocar site infection in three, urinary retention in six and neuralgias in five.

In conclusion, totally extraperitoneal approach to laparoscopic herniorraphy has acceptable recurrence and complication rates which makes it a very good alternative to conventional hernia repairs.

Local anaesthesia and ambulatory outpatient surgery for inguinal and femoral hernia repair using the Trabucco technique

G. Campanelli, R. Cavagnoli, G. Gattei, L. Bottero, M. De Simone, F. Gabrielli and P. Pietri *Department of General and Thoracic Surgery, University of Milan, Hosp. Maggiore Policlinico, Via Francesco Sforza, 35, 20122 Milan, Italy*

In the last few years there have been various attempts to improve and increase utilization of highly specialized hospital facilities. The main purpose has been the reduction of cost Ambulatory outpatient surgery has increased the provision of surgical services Using modern prosthetic materials (mesh and plug) it is now possible to manage all hernia repairs without distorting normal body anatomy and avoiding tension. The Lichtenstein method and modified by Trabucco has four principles, (a) tension-free, (b) prosthetic materials: plug and mesh, (c) routine local anaesthesia, (d) get up and go The technique proposed is simple, efficient, characterized by a rapid procedure, giving an excellent clinical outcome: postoperative pain is low permitting the patient to resume normal physical activities in a short time Local anaesthesia offers early mobilization, a reduction of costs, decreased hospital stay and improved bed availability for other patients on the waiting list Besides the undeniable economic advantages, local anaesthesia is safer than other types of anaesthetic management We employ three different types of plug. We use a parachute plug (Pch) that has a better capacity to open giving wider support to the internal ring in the repairs of inguinal indirect hernias. The plug T2 is utilized for recurrent hernia repairs by a preperitoneal approach and for primary femoral hernias It is made up of a plug T1 fixed with four polypropylene stitches to a polypropylene monolayer base giving an area larger than the plug itself In more extensive recurrences in addition to the T2 plug a marlex square (about 15 cm × 15 cm) is used posteriorly to T2 on the preperitoneal plane From

January 1992 to May 1996 at the Department of General and Thoracic Surgery of Milan University, 1090 hernia repairs were performed in 1042 patients; 911 (83·5 per cent) of whom underwent ambulatory outpatient hernia surgery. Of the remaining 131 patients, for whom in patient surgery was required, 121 (11·6 per cent) were treated by general anaesthesia and 10 (0·9 per cent) by epidural anaesthesia; 748 patients underwent a surgical repair in the period January 1992 to May 1995; 598 (80 per cent) were contacted by telephone and then visited for a control. Out of these, 490 (82 per cent) had undergone an outpatient ambulatory surgical repair. Only five (0·8 per cent) patients complained of postoperative neuralgia lasting longer than 3–6 months. Two recurrences were found after surgery for recurrent hernias and only one after primary surgery

Shouldice *vs* Lichtenstein technique of inguinal hernia repair: preliminary results of a multicentric randomized prospective trial

C. Castoro, P. Polo, M. Pignataro, P. Sorrentino, G. Spreafico, U. Baccaglini, E. Ancona and Hernia Study Group* *University of Padua, Italy, 2nd Department of General Surgery, Ospedale Busonera, Via Gattamelata, 64, 36128 Padova, Italy*

Aim: To compare results and outcomes following Shouldice and Lichtenstein tension-free inguinal hernia repair performed in Departments of General Surgery and Teaching Hospitals.

Methods: Between May 1994 and December 1995, 383 patients with primary unilateral inguinal hernia were randomized to have Shouldice (Group S) or Lichtenstein (Group L) herniorraphy Different anaesthesiological techniques have been used. Postoperatively patients completed pain and activity visual analogue scales, and use of analgesia was recorded A questionnnaire of quality of life has been administered to all patients a week before and a week after the operation. Complications, duration of hospital stay, time of return to normal domestic activity and to work were assessed. Postoperatively, patients were followed up in clinic at 1 week and 3 weeks Long-term follow-up has been planned every 6 months for at least 3 years Preliminary results in the first 155 patients randomized have been analysed Results of the whole group of randomized patients will soon be ready

Results: The groups were similar for age and sex. Non-opioid analgesia was administered in about 40 per cent of patients in both groups Overall mean pain analogue score after one week was 18·9 for Group S and 13·7 for Group L. Overall mean activity analogue score after one week was 52·7 for Group S and 49·3 for Group L. Minor complications including haematomas and paresthesias occurred in 23 per cent of patients in Group S and 18 per cent in Group L. Return to normal activity after 3 weeks was over 80 per cent in both groups of patients. Immediate postoperative complications occurred in eight patients four haematomas and four urinary retensions.

Conclusions: No major complications have been recorded with both techniques Less pain and earlier return to work was associated with Lichtenstein technique.

***Hernia Study Group:** Baggio E., Busso A., Corsini A., Corso G.F., Franceschini M., Frasson P., Furlani S., Galeotti F., Gracco L., Lipari G., Mariotti R., Munegato G., Nosadini A., Omodei Salè S., Pagani M., Rizzo C., Roviaro G.C., Sicari U., Spina G., Tasinato R., Tremolada C., Vairani G., Viani M.P., Varoli F., Vecchioni R., Zaffin M., Zotti E.F.

Obturator hernia as an uncommon cause of intestinal obstruction

J.B. Comes, F. Guspí, A. Sánchez Marín, J. Sánchez Pérez, J J Sánchez Cano, J Domènech, J. Jara and D. Del Castillo Déjardin *Department of Surgery, Hospital Universitari de Sant Joan de Reus, Spain, Universitat Rovira i Virgili, Spain*

Introduction: Obturator hernia is a rare cause of intestinal obstruction The hernia's rarity makes diagnosis difficult and increases mortality. In the past 15 years, four patients with incarcerated obturator hernia were seen at our Department

Patients and methods: We have reviewed all the patients operated in our department with incarcerated obturator hernia. All of them were women, with a mean age of 88 years Three of them presented a subacute small bowel obstruction, that delayed treatment for a week. Only one case was admitted with a complete obstruction, and underwent surgery in the first 48 h Three cases had previous symptoms of pain in the hip or the medial aspect of the thigh, and the classical sign of Howship–Romberg, characteristic of this process, was not seen. Except in one case, initial blood analysis showed a left shift to a leukocytosis, and in all of them an increased plasma urea. Abdominal X-rays revealed slightly dilated loops of small intestine and, in only one case, radiological signs of complete obstruction. Diagnosis was made at the time of the operation in all four cases. We found three right obturator hernias and one bilateral hernia. In this case, intestinal strangulation involved a Meckel's diverticulum at the right side. In other two cases there was a Richter type of hernia Two patients required resection of non-viable intestine. Closure of the hernial defect was performed in all the cases One patient died postoperatively of multiorganic failure. Postoperative complications included one wound infection and one urinary tract infection. Mean postoperative hospital stay was 3 weeks

Conclusions: Although obturator hernias are rare, they should be considered when an elderly female patient presents with a bowel obstruction. Active testing for the Howship–Romberg sign could be a simple method to achieve an early diagnosis and surgical intervention, both essential in order to reduce the morbidity and mortality related to this process.

Repair of incisional hernia by the Rives technique

A. Martín Duce, J.M. Muguerza, T. Ratia, A. Gutiérrez, M. Díez, R. Villeta, E. Tobaruela, F. Noguerales and J. Granell *Príncipe de Asturias University Hospital, Service of General Surgery, Ctra. Alcalá-Meco s/n, 28805-Alcalá de Henares, Madrid, Spain*

Introduction: Despite new developments in both suture and prosthetic materials, incisional hernia remains an important complication of surgery involving the abdominal wall The rates reported by different authors range from 2 per cent to 11 per cent The use of prosthetic materials is now considered the best technical choice for incisional hernias of moderate to large size, avoiding the main cause of failure: a tension repair Rives bases his technique in two principles the true loss of abdominal wall in any hernia with a defect greater than 5 cm and the lateralization of the rectus muscles in midline hernias Therefore, any repair should meet two essential criteria· the use of a mesh that substitutes the parietal loss and the return of the rectus muscles to the midline.

Patients and methods: Between 1992 and 1995, 50 incisional hernias were reconstructed in 50 patients. All except one (who received a PTFEe patch) were repaired with a multifilament polypropylene mesh (Surgipro). There were 22 men and 28 women with a mean age of 55 years Nine patients had been previously operated between two and five times. The size of the hernias ranged between 10 × 5 and 25 × 15 cm. All patients were operated on according to the technique described by Rives. No patient was lost in the follow-up. All patients were inspected every 4 months during the first year and annually thereafter. In nine patients a cosmetic dermolipectomy was performed in addition through a Pfannestiel incision during the same procedure. To avoid errors of clinical detection during follow up, all patients ($n = 9$) 30 per cent obesity (BMI > 32 m^2/kg) were submitted to CT scan.

Results: The follow-up ranged from 6 to 40 months with a mean of 24·5 months. There was no mortality. The postoperative morbidity was 32 per cent. Early postoperative complications were. localized abdominal wall necrosis ($n = 3$), seroma ($n = 5$), local infection ($n = 4$), subcutaneous haematoma ($n = 2$), ileus ($n = 1$), and deep vein thrombosis ($n = 1$). In all cases of infection *Staphylococcus aureus* was cultured. Systemic antibiotics resolved the local infection in three cases and in the other a PTFEe patch had to be removed 1 month after the operation Late complications were sinus ($n = 2$) and lateral abdominal wall pain in the area of the semilunar line ($n = 11$). There were no hernia recurrences.

Discussion: Three of the four cases of local infection had a wound infection in the previous operation, the same type of bacteria being cultured. These data are similar to those reported in the literature and could be explained by the activation of bacteria that remained quiescent, triggered by the immunity impairment generated by the surgical injury. It is also noteworthy that the high percentage of pain in the lateral abdominal wall was at the Spiegelian point. This late complication, rarely quoted in the literature, has been reported by Rives in 25 per cent of his patients. Excessive tension from the anchoring non-absorbable stitches that fix the mesh to the abdominal wall could be the explanation Perhaps the use of slowly reabsorbable sutures to ensure fixation for at least the 120 days of staples or a biological glue, could prevent this sometimes disabling pain.

Conclusion: The Rives technique has proved satisfactory for the reconstruction of large abdominal wall defects. Although it is a complex technique not free of morbidity, the low recurrence rate makes it a valuable tool for incisional hernias

Tension-free hernioplasty in inguinal hernias

H. Gökbayır, K. Kılıç, F. Ercan and E. Ozdemir *Bayındır Medical Centre, Soğütözü, Ankara, Turkey*

In our study, 156 patients with inguinal hernias who were treated with tension-free hernioplasty in Bayındır Medical Centre, between November 1993 and February 1996 are reviewed. The longest follow-up period was 28 months and shortest was 2 months One hundred and twenty-three patients were males and 33 were females In 12 patients there were bilateral inguinal hernia; 93 of the hernias were direct and 75 were indirect hernias. The hernias were recurrent in 11 patients. In 101 patients haemovac drains used for drainage. In eight cases among 55 patients in whom no drainage device was used postoperative wound haematomas occurred, but all of these haematomas disappeared with medical treatment There were no early complications in the group where haemovac drainage was used No hernia recurrence was detected during the follow-up period

In our opinion tension-free inguinal hernia repair is a safe, easily applicable method that has to be the preferred technique because of its low complication and recurrence rates

Local anaesthesia for groin hernia repair

N.N. Gonullu, N Z. Canturk, N.Z. Utkan and M. Dulger *Kocaeli University, School of Medicine, Department of General Surgery, Kocaeli, Turkey*

Appropriate anaesthesia during operations must provide maximum confidence for patients and optimum surgical conditions for surgeons Selection of anaesthesia type is connected with patients' conditions. In particular, chronic diseases of aged patients are important factors for selection of anaesthesia

Patients' ages were ranged 45 to 84 years (mean 56·6 years) Indirect hernia were the most frequent hernia type in this series, 38 (88 per cent), five (12 per cent) direct hernias. The patients were premedicated with 100mg intramuscula pethidine 1h before Intravenous access was obtained prior to surgery and during the procedure, and patients were monitored

Prilocain (2 per cent) with adrenaline were diluted normal saline and used as a field block starting just medial to the anterior superior iliac spine The solution was injected in three different directions through anaesthetized skin, transversely toward the umbilicus, parallel to the inguinal ligament and through the incisional line Subfascial infiltrations were placed deep to the internal inguinal ring, to the pubic spine along the line of inguinal canal and to the rectus sheet If necessary, local anaesthetic was infiltrated around the internal ring during surgery. Repairs used were a modified Bassini for 27 patients, and Shouldice for 16 patients

The mean duration of surgery was 52min (range 35–75min). Postoperative complication such as haematoma, wound infections, and seroma were found in three patients (7 per cent). Patients were discharged at a mean of 3 days (range 6h–18 days) after surgery and no recurrences were seen

In conclusion, we suggest that local anaesthesia for groin hernia repair is a feasible, cost effective and a safe technique for the repair of inguinal hernias

Outpatient inguinal hernia repair

R Krupiński, J Narębski, J Tazbir, L Pomorski, J. Ganczarski and M. Bartos *Surgery Clinic of the Endocrinology Institute of the Medical University of Łódź, Copernicus-Hospital, ul. Pabianicka 62, 93-513 Łódź, Poland*

Aim: The presentation of a method and results of outpatient inguinal hernia repair

Materials: In the years 1994–1995, 480 patients were operated on for inguinal hernia, including 136 (91·9 per cent) males and 12 (8·1 per cent) females. The age of the patients ranged from 18 to 64 years (mean 47 years). Ninety-seven (65·5 per cent) indirect and 51 (34·5 per cent) direct hernias were discovered at operation. After intramuscular premedication with the use of pethidine, promethazine and atropine, the patients were operated on under local anaesthesia (0·5–1 per cent lidocaine) Ninety-two (62 per cent) patients underwent Bassini operation and in 56 (38 per cent) Shouldice herniorrhaphy was used Of the operations 75·7 per cent were performed on a day case basis

Preoperative investigations were conducted in the outpatient departments. The patients were admitted to the clinic in the morning, operated on in the afternoon and discharged 4–8h (median 6h) after the procedure Two (2 per cent) developed a haematoma, three (3 per cent) experienced scrotal oedema, and in one (1 per cent) wound infection occurred Over the follow-up period ranging from 6 to 24 months no hernia recurred There were no significant differences between the incidence rates of early and late complications in both groups of the patients

Conclusions: Day case repairs of uncomplicated inguinal hernia are as safe and effective as herniorrhaphy performed upon in patients

Incidence of incisional hernia in surgically treated morbidly obese patients

G Ortega, F. De la Cruz, S. González, P. Yuste, R Gálvez, J.I Martínez, C. Pérez and J.M. Menéndez *General and Digestive Surgery Service A, '12 de Octubre' Hospital, Complutense University, Madrid, Spain*

Introduction: Obesity has traditionally been considered a major risk factor in the development of incisional hernia We review the incidence of incisional hernias following laparotomy in a group of patients operated on for morbid obesity and their relation to other risk factors.

Patients and methods: We retrospectively studied 55 patients (47 women and 8 men) operated on for morbid obesity since 1986 Mean age was 40 years old. Preoperative average weight was 130kg and average height was 159·7cm. Midline supraumbilical laparotomy was performed in 87 per cent of cases ($n = 48$) Twenty-one patients (38 per cent) had a previous laparotomy The abdominal wall was closed with a mass technique in 50 per cent of patients and with a layered technique in the other half. Eighty-three per cent of patients ($n = 46$) received preoperative antibiotic prophylaxis with a first generation cephalosporin

Results: Incisional hernia incidence in this series is 20 per cent ($n = 11$) Half of the cases occurred in patients with a previous laparotomy In 80 per cent ($n = 44$) of incisional hernia cases, the closure procedure performed was a layered technique No eviscerations occurred Surgical wound complications were as follows: infection ($n = 2$), seroma ($n = 3$), haematoma ($n = 2$) and skin dehiscence ($n = 5$). Only one case of incisional hernia was observed in this group

Conclusions: We conclude that in this series, abdominal wall closure technique and a previous laparotomy are the most significant risk factors for the development of an incisional hernia in severely obese patients in patients undergoing laparotomy

Hernioplasty: Trabucco *vs* Bassini—our experience

G. Pagano, L. Persico Stella and M. Di Domenica *General Surgery Division, 'S. Giuseppe' Hospital A, USL RM H Albano Laziale, Rome, Italy*

The advent of the tension-free hernioplasty is a real development in the treatment of groin hernia. Until August 1991 in our department we had performed hernioplasty using a Bassini repair in the great majority of cases Since then we have performed hernioplasty with the polypropylene mesh plug as described by Trabucco. In this paper we compare the results of our last 5 years of our experience using Bassini's technique with the results obtained during the first 5 years of using Trabucco's technique. From 1986 to 1991 we performed 492 Bassini herniorrhaphies, 475 by routine and 17 as emergencies, the patients had a mean age of 49·8 years (range 6–94 years). The operations were mainly performed with general anaesthesia, with an average hospital stay of 6·8 days. The recurrence rate was 3·2 per cent Since August 1991 we have performed 549 Trabucco operations, 504 routine and 45 emergencies, mean age 57·9 years (range 6–92 years). We have not had any postoperative complication. The operations have been carried out mainly under spinal or local anaesthesia and have an average hospital stay of 2·1 and 1·7 days respectively Today with a 2-year follow-up on 80 per cent of the patients we have found three recurrences. We can conclude that, in our experience with both Bassini's and Trabucco hernioplasty that the latter achieved better results.

Surgical treatment of strangulated femoral hernia

D. Palomares, I. Rodríguez, A. Chames, A. Aranzana, F. Jiménez and E. Bengoechea *Surgery Department, 'Virgen de la Salud' Hospital, Toledo, Spain*

The preperitoneal approach is a good method to repair unilateral or bilateral femoral hernias, specially in complicated cases. During the last 10 years we have used the preperitoneal technique in emergency surgical treatment of femoral hernias.

We use a transversal incision to explore the preperitoneal space. We reduce and open the femoral hernial sac to allow inspection of its contents. The repair of the hernia begins with high ligation of the sac. Hernioplasty is achieved by suturing the iliopubic tract and the posterior margin of Cooper's ligament with non-absorbable sutures. One hundred and twenty patients have been operated on because of complicated femoral hernia (incarcerated or strangulated). The majority of these patients were elderly women. We performed intestinal bowel resection in 38 cases. Postoperative complications occurred in 21 patients. We reoperated because of intestinal perforation or peritonitis from which three patients died. Four patients developed recurrences.

Conclusions: The preperitoneal approach is a good surgical technique for the repair of complicated femoral hernias which has low morbi-mortality and few recurrences

The influence of postoperative stay on the results of inguinal hernia repair

M.M. Pellicer, A. Escartín, M.D. Arribas, J.J. Resa, A. Val-Carreres, M.A. Bielsa and M. González *Department of Surgery, University of Zaragoza Hospital, Spain*

Introduction: Inguinal hernia repair is practised in most of the world's hospitals. It imposes a substantial cost, that can be considerably reduced without reducing the quality of medical care.

Material and methods: We present a review of 172 patients treated over 4 consecutive years, with a minimum follow-up of 2 years. Male patients with primary indirect inguinal hernias were selected for study The mean age was 56·7 ± 1·8 years Bassini repair (BR) was performed in 82 cases (47·7 per cent) and Lichtenstein repair (LR) using a polypropylene mesh in 90 cases (52·3 per cent). Two groups have been analysed according to postoperative stay: short stay (SS) less than 48 h (94 patients, 54·6 per cent) and long stay (LS), kept in hospital until the skin suture removal (78 patients, 45·4 per cent). Antibiotic prophylaxis was used in accordance with our hospital's protocol.

Results: Ratio between BR/LR was 44 per cent/56 per cent in SS and 53 per cent/47 per cent in LS. Operative anaesthesia was local in 57·4 per cent ($n = 54$) of SS and in 6·4 per cent ($n = 5$) of LE ($P < 0·05$). Operating time was 64 min in SS and 68 min in LS ($P > 0·05$). The mean post-operative stay varied from 0·9 days in SS and 6·7 days in LE. Complications were presented in 13·8 per cent ($n = 13$) of SS and 33·3 per cent ($n = 26$) of LE ($P < 0·05$). When antibiotic prophylaxis was practised, infection rate was similar among SS (4·2 per cent, $n = 2$) and LS (5·3 per cent, $n = 1$), while in the cases in which it was not used. Infections occurred among SS ($n = 1$, 2·1 per cent) and LS ($n = 8$, 13·6 per cent) ($P < 0·05$). Postoperative pain presented 4·2 per cent ($n = 4$) in SS and 1·3 per cent ($n = 1$) in LS ($P > 0·05$). Recurrence at 2 years was 2·1 per cent ($n = 2$) in SS and 6·4 per cent ($n = 5$) in LS ($P > 0·05$).

Conclusions: The important economic saving obtained with early hospital discharge has been associated with less morbidity, especially wound infection, without differences in either postoperative pain or recurrence rate.

Groin hernia: totally preperitoneal laparoscopic surgery *vs* open (Stoppa) procedure: prospective randomized trial 100 cases

N. Rizk, J.M. Catheline, H. Riskalla and G. Champault *Hôpital Jean Verdier, 93140 Bondy, France*

In a prospective randomized trial between totally preperitoneal (TPP) laparoscopic surgery and Stoppa procedure (open), 100 patients with groin hernia (Nyhus IIIA, IIIB, IV) were included and followed over 3 years. Both groups were comparable.

In the laparoscopic group, operating time was significantly longer ($P = 0·01$) but hospital stay (3·2 *vs* 7·3 days) and delay to return to work (17 *vs* 35 days) were significantly reduced ($P = 0·01$). Postoperative comfort (less pain) was better ($P = 0·001$) after laparoscopy. In this group, morbidity was also reduced (4 per cent *vs* 20 per cent, $P = 0·02$).

The mean follow-up was 605 days and 93 per cent of the patients were reviewed at 3 years. There were three (6 per cent) recurrences after TTP, especially in the beginning of the surgeon's experience (learning curve) versus none for the Stoppa (n.s.) In case of bilateral hernia, the authors suggest the use of a large prosthesis rather than two little ones to prevent recurrences.

In these conditions, laparoscopic (TPP) approach of groin hernia treatment will have the same recurrence rate as open (Stoppa) procedure, but a real advantages in the early postoperative period.

First experience in laparoscopic groin hernia repair

J. Stanaitis and R. Rūkas *General Surgery Clinic, 2043 Vilnius University Emergency Hospital, Lithuania*

The advantages of laparoscopic hernia repairs (LHR) in the treatment of inguinal hernias has been shown in surgical practice. The aim of this study was to analyse the LHR results itself as well as early postoperative recurrences.

Patients and methods: In February 1994 LHR were initiated at Vilnius University Emergency Hospital. In total 22 LHR were carried out up to January 1996 including 17 one side and five bilateral inguinal LHR (four females, 18 males, mean age 48·1 years, range 17–77 years). All patients were operated on under general anaesthesia Fifteen indirect as well as 11 direct inguinal hernias were followed up in the postoperative period. Among them four cases were found to be recurrences after the open herniorrhaphy Twenty-four transabdominal praeperitoneal LHR and three preperitoneal LHR were done using non-absorbable prolene mesh in all cases The size of the mesh used for the first 15 operations was not sufficient to close completely the defects of femoral, direct and indirect inguinal hernias. An increase of mesh size up to 14 × 9cm improved defect closure. Postoperative stay was 3·8 days Patients were followed up for 3 to 6 months after surgery.

Results: We had one complication inferior epigastric vessel damage, which was managed laparoscopically In four out of 22 patients recurrence developed. All recurrences occurred in the first 10 LHR between 2 days to 3 months after surgery. Presumably the recurrences were related to the incorrect size of the mesh as well as lack of experience.

Conclusions: A comfortable postoperative state and a short time in hospital produced quick recovery. The relatively high incidence of recurrence seems related to mesh size and surgical experience A 14 × 9cm mesh is recommended.

Conventional *vs* open 'tension-free' hernioplasty: preliminary results of a prospective multicentre randomized trial

M P. van den Tol, D.C.D. de Lange, R.W. Luijendijk, A.B. Rottier, D. van Geldere, P.A. Vegt, W.C.J. Hop, J.N.M IJermans and J. Jeekel *Department of General Surgery, University Hospital-Dijkzigt, PO Box 55, 3000 WB Rotterdam, The Netherlands*

Aim: To determine whether Lichtenstein 'tension free' hernia repair can surpass an established open method, especially in terms of recurrence, at acceptable costs.

Design: A prospective, multicentre, randomized trial

Patients and methods: Between September 1993 and January 1996, 300 patients aged older than 18 years (mean age 55 years) having a unilateral primary inguinal hernia were randomized to undergo either an established open hernia repair or a Lichtenstein 'tension-free' hernia repair using polypropylene meshes Patients with bilateral hernias and patients who had previously taken part in this study were excluded Patients were seen 1 week and 1 month after operation and thereafter every 6 months for 3 more years Parameters studied included operative and discharge times, morbidity, time after which patients returned to work, major costs and recurrences

Results: Five patients were withdrawn from the study after inclusion, two underwent a laparoscopic hernia repair; three patients had a femoral hernia. Of the remaining hernias 47 per cent were left, 53 per cent were right; 32 per cent were medial, 49 per cent were lateral and 19 per cent were combined. Fifty-one per cent underwent an established (A) and 49 per cent a 'tension-free' (B) repair Both groups were well matched for all baseline parameters. In both groups 62 per cent underwent total, 23 per cent epidural and 15 per cent spinal anaesthesia There were no statistical differences concerning operation time (44 *vs* 48min), postoperative complications such as haematomas, wound infections or wound dehiscences, postoperative comfort (pain scores were used) and hospital stay (mean 2 days) between the two groups. There was a statistical significant difference in the postoperative appearance of seromas, 6 per cent in Group A and 14 per cent in Group B ($P = 0\ 049$, Fisher exact). Return to normal daily activity was not significantly different between both groups In Group A patients returned to work after 22 (mean) days and in Group B after 21 days The quality of life did not differ significantly between the two groups at any point during follow-up, all patients had a significantly higher quality of life 1 month after the operation in comparison to their life quality before and 1 week after the operation Major costs (operative time, hospital stay, and time before returning to work) were not significantly different between both groups During a mean follow-up time of 13 months only one recurrence appeared in Group A.

Conclusions: The short-term results of both operative techniques were similar for all parameters studied except for development of seromas The 'tension-free' hernioplasty is a safe procedure that can be performed under different sorts of anaesthesia. Further follow-up will have to be awaited to draw conclusions on long-term recurrence rates.

e-PTFE darn: a traditional technique for the inguinal hernia repair

G. Velmachos, C. Kindylidis, A. Mystakidis, G Svoronos, F. Seferiadis, G Dimitrakakis, A. Souvatzoglou and M. Tsitsirikos *Sotiria General Hospital of Athens, 115-26, Athens, Greece*

Laparoscopic herniorrhaphy requires continuous ongoing evaluation of safety and efficacy. Long-term results with this repair will not be known for several years. As the benefits of extending laparoscopic techniques to inguinal hernia repair are unclear, the traditional repairs will remain in use. The aim of the present study, is to report our 5-year experience in the repair of inguinal hernia, using 'e-PTFE darn', a traditional technique A total of 423 patients, 21–72 years old (mean 52·7 years), underwent unilateral elective inguinal repair, 92 for direct and 331 for indirect inguinal hernias using an e-PTFE darn technique The technique is a Moloney's nylon darn modified by us in two respects; instead of the nylon suture, a monofilament suture is used, made from expanded polytetrafluoroethylene (e-PTFE), in addition, the transversalis fascia is reinforced by an interlacing e-PTFE suture, after closure of the internal ring using the same suture. Postoperatively we have observed a suture sinus formation in one patient (0·23 per cent), deep sepsis and discharging haematoma in two patients (0·47 per cent), superficial wound infection which was healed without complication in five patients (1·18 per cent), and recurrence in three patients (0·70 per cent). None of the patients developed symptoms of inguinal nerve entrapment or testicular swelling. The average postoperative stay was 3 5 days. All patients were followed up for more than 5 years after the operation. We conclude that e-PTFE darn, a traditional technique, gives a low rate of postoperative complications and recurrence.

Surgical treatment of incisional hernias: analysis of 1847 cases over a period of 25 years

J. Vidal, J. Comajuncosas, J. Janer, F. Mora, M.A. Garcés, K.J. Olsina, A. Flor and J. Olsina Pavía *Hospital General Vall d'Hebron, Pº Vall d'Hebron 119-129, 08035 Barcelona, Spain*

Aim: To present 25 years of experience in surgical treatment of 1847 incisional hernias

Materials and methods: From January 1970 to December 1995, 1835 patients with 1847 incisional hernias underwent surgery: 1266 (69 per cent) were women and 569 (31 per cent) men. Two hundred and ninety-six (16 per cent) were spontaneous (all of them diastatic) and 1551 (84 per cent) traumatic [1475 (79·9 per cent) postoperative and 76 (4·1 per cent) accidentals]. Taking into account sac size, the diameter of the orifice and the quality of the edges, the following procedures were performed: closure by simple suture, aponeurotic or myoplasties and mesh reinforcement.

Results: A 25 per cent recurrence was found with simple sutures, 6 per cent with the use of abdominoplasty and 3 per cent when a reinforcing mesh was used.

Conclusions: After 25 years of experience the use of a reinforcing mesh is now advocated.

Topical antibiotic prophylaxis in herniorraphies using prolene mesh

H. Yavuz, N. Sirolu, M. Bayrak, G. Ozdemir and N.A. Kama *4th Department of Surgery, Ankara Numune Hospital, Ankara, Turkey*

Aim: Many repair techniques have been described for hernias, but recurrence continues to be an important issue New approaches have been tried, including the use of a mesh prosthesis. However, there are concerns that these prostheses may become infected or cause a foreign body reaction We have planned this prospective study to assess the risk of infection and to examine the effect of topical antibiotic prophylaxis

Material and methods: Fifty patients were taken into the study at 4th Surgical Clinic of Ankara Numune Hospital. The patients were divided randomly into two groups There were 26 patients in the first group (three females, 23 males), with an average age of 52 years In 18 patients, unilateral inguinal hernia, in five bilateral inguinal hernia and in three, incisional hernia was present. In the first group, 18 patients had anterior mesh herniorraphy, four had a Stoppa procedure, one had bilateral anterior mesh herniorraphy and three had primary repair plus onlay mesh herniorraphy There were 24 patients in the second group, with an average age of 45 years. In 18 patients unilateral inguinal hernia and in six, bilateral inguinal hernia were present In the Stoppa procedure and one had bilateral anterior mesh herniorraphy, polypropylene mesh was used in all patients. In the first group 1g antibiotic (sulbactam + ampicillin) was topically applied over the mesh placed on the posterior wall of inguinal canal. No antibiotics were used in the second group.

Results: In the first group, cord oedema developed in one patient on postoperative day 1, scrotal support was used and oedema resolved on postoperative day 5 Wound infection developed in one patient on day 5 (4 per cent), the wound was opened and systemic antibiotics were started. The infection improved on day 13 and the wound was sutured No infection developed in any patient in the antibiotic group. In addition, no local or systemic adverse effects were observed due to antibiotic usage. One patient had wound infection in the second group.

Conclusion: There was no difference in the rate of developing infection between the two groups. It is thought that topical antibiotic prophylaxis may not be necessary in prolene mesh herniorraphies.

Infection, Sepsis & Wound Healing

Sepsis of abdominal origin, treatment with piperacillin/tazobactam

M. Aizcorbe, R. Trujillo, F. Cobo, A Diaz de Liaño, N. Moras, M. Ciga, C. Yarnoz and M. Cires *General Surgery Department, Virgen del Camino Hospital, Irunlarrea 4, Pamplona 31008, Spain*

Postoperative abdominal sepsis is a serious complication which results in increased morbidity and mortality Due to this, surgical teams have developed special interest in controlling and preventing all the possible causes of sepsis and establishing early and aggressive treatment when suspected

Material and methods: Fifty patients (29 males and 21 females) were treated during 18 months due to suspected–confirmed sepsis of abdominal origin. Mean age was 60 years. Therapy consisted of piperacillin-otazobactam 4·5g/8h/i v. Treatment was continued for 2 more days after the symptoms had disappeared Mean therapy duration was 8·5 days (6–14 days). All patients received preoperative prophylactic treatment with either 1g cephotaxime and 500mg metronidazole or 1g cephonicid.

Diagnosis: See Table 1

Anastomotic leak in malignant disease	18
Anastomotic leak in benign disease	4
Biliary sepsis	9
Intra-abdominal abscess	7
Pelviperitonitis	6
Postcystopericystectomy residual cavity infection	2
Postoperative pancreatitis	2
Hepatic trauma	1
Intestinal ischaemia	1

Results: Clinical response was as follows: failures· 3; could not be assessed: 6; change in antibiotic· 1, cured/recovered: 40 Secondary effects were one pruritus and palpebral oedema where the antibiotic was changed No analytical alterations were related to antibiotic therapy Of the 50 patients, 46 'significant' samples for microbiological study were obtained from 38 patients (32 fluid/peritoneal pus; 11 blood cultures, three pleural effusions) with the following micro-organisms: 19 Gram-positive bacteria; 13 Gram-negative bacteria; three anaerobes and two *Candida* sp.

Conclusions: Combined and aggressive management for postoperative abdominal sepsis must always be carried out (antibiotics, early re-operation, percutaneous drainage of collections, supportive measures, etc) Antibiotic treatment with piperacillin/tazobactam was effective in 80 per cent of the cases.

An early indicator in sepsis: the β-hydroxybutyric acid to acetoacetic acid ratio

G. Antsaklis, S. Pierrakakis, P. Karydakis, N. Economou, G Marinakis and D. Douridas *Surgical Department, Sismanoglion General Hospital, Athens, Greece*

It is well known that in patients with sepsis the mortality is high, sometimes close to 70 per cent, mainly in the presence of lung damage (ARDS). Sepsis is documented in approximately 10 out of every 1000 hospitalized patients In sepsis as CO_2 consumption is reduced, energy production is by oxidation of free fatty acids, resulting in increased levels of NADH. These levels inhibit the Krebs' cycle causing an increase in β-hydroxybutyric acid levels. The oxidative phosphorylation pathway is also inhibited, producing a further increase in β-hydroxybutyric levels. The purpose of this study was to measure the ratio of β-hydroxybutyric acid to acetoacetic acid as an early indicator of sepsis or MOF. We studied 30 patients (18 males and 12 females), with a mean age of 57·8 years, who were septic. Blood samples were taken twice daily at the same time, every day and β-hydroxybutyric and acetoacetic acid were measured until they died or recovered from sepsis It was found that patients who survived had a mean value of the ratio 1·4 + 0·43, while patients who died had a mean value of 3·5 + 0·94 ($P < 0·001$). We found statistically significant difference ($P < 0·05$) between the patients who developed MOF (ratio > 2·5) and the ones in whom sepsis was the main problem (ratio < 2·5), only six patients developed hepatic, renal or respiratory failure. We believe that β-hydroxybutyric/acetoacetic acid ratio could be a good indicator in detecting early sepsis and MOF as well as in the prognosis.

The effects of glutathione depletion in endotoxaemic organ injury

B. Bozkurt*, M. Koç*, O. Cengiz*, E. Demirpençe‡, K. Kilinç‡ and F. Aksoy† **Numune Hospital 2nd General Surgery Clinic and †Department of Pathology, ‡Hacettepe University, Faculty of Medicine Department of Biochemistry Ankara, Turkey*

In endotoxaemia, many factors seriously disturbing blood circulation trigger multiorgan injury due to free radical generation. Glutathione (GSH) is one of the major endogenous antioxidants, protecting tissues against free radical injury. Using different doses diethylmaleate (DEM), (Group 1 no medication, Group 2: 2ml 0·9 per cent NaCl + 1μg/g endotoxin*; Group 3: 1μg/g DEM + 1μg/g endotoxin*, Group 4: 2μg/g DEM + 1μg/g endotoxin were injected intraperitoneally) we produced different levels of GSH depletion in rats which were further subjected to experimental endotoxaemia (*Two hours later *E. coli* O26.B6 endotoxin was used, Sigma Chem Comp.) Oxidative injury in liver, kidneys, ileum, brain and lungs was examined histopathologically and evaluated biochemically Reduced and total GSH, lipid peroxidation (malondialdehyde, MDA), lactate and hypoxhantine levels were compared between groups. Also the results were compared to both sham and endotoxaemic control groups. Histopathological examination showed pronounced injury in the liver, kidneys and ileum of the endotoxaemia group compared to the sham group and the injuries were even more prominent in the GSH depleted groups. There were no injury to brains in any group In biochemical evaluation, total and reduced GSH levels were decreased in GSH-depleted groups, MDA and hypoxanthine levels were higher in the GSH-depleted groups. MDA and hypoxanthine levels were higher in the endotoxaemia group than in the sham group and in the GSH depleted groups these were also higher than the endotoxaemia group. Interestingly high lactate levels were found in the endotoxaemia group but low levels in the GSH-depleted groups. It was suggested that advanced membrane injury facilitated the loss of lactate by diffusion through the membrane and in contrast, the cells selectively retained hypoxanthine for a longer time.

Evidence of local production of nitric oxide and carbon monoxide in patients with acute peritonitis

J. Calatayud, J. Arias-Diaz, J. Hernandez, J. Torres-Melero, A del Real, E. Vara and J.L Balibrea *Department of Surgery, Hospital San Carlos, and Department of Biochemistry, Faculty of Medicine, Universidad Complutense, Madrid, Spain*

The production and effects of cytokines are generally confined to organic compartments Therefore, in peritonitis the effects of tumour necrosis factor (TNF-α) should be more apparent within the peritoneal cavity than elsewhere. There is increasing evidence that endogenous synthesis of nitric oxide (NO) and carbon monoxide (CO) mediate some TNF-α effects during inflammation. We have investigated the local production of these mediators during peritonitis and whether there is systemic spillover from the peritoneal cavity during this condition For that we obtained simultaneous plasma and peritoneal fluid samples of a group of 23 patients undergoing surgery for acute peritonitis (acute appendicitis or gastrointestinal perforation). Control group was made up of 10 patients operated upon for acute abdominal condition although without peritoneal infection. After centrifugation and −80°C storage, TNF-α (ELISA), NO_2^- + NO_3^- (Griess reaction), CO and myeloperoxidase (spectrophotometric method) were measured. In peritoneal fluid of peritonitis patients we found increased levels of TNF-α (169·7 ± 38·3, *n* = 18, *vs* 51·2 ± 45·8, *n* = 8, pg/ml, *P* < 0·01), NO (21·1 ± 4·7, *n* = 18, *vs* 10·2 ± 1·1, *n* = 8, nmol/ml, *P* < 0·05), CO (69·7 ± 2·0, *n* = 22, *vs* 33·7 ± 1·4, *n* = 10, *P* < 0·001), and myeloperoxidase, a marker of neutrophil activation (15·0 ± 1·8, *n* = 18, *vs* 9·3 ± 3·3, *n* = 8, *P* < 0·05), when compared to controls. In contrast, there were no differences in the plasma levels of the above mediators between both groups of patients. We can conclude that in human peritonitis there is increased local production of TNF-α, NO, and CO, without concomitant increase in the plasma levels of these mediators

Comparative study of free radicals scavenging activity between allopurinol and uric acid

M.L. Delgado, J.A. Ferrón, S.A. Delgado, A. Collado, M.C. Ramirez and D. Garrote *Virgen de las Nieves Hospital, Unit of Experimental Surgery, Coronel Muñoz Street, 18014 Granada, Spain*

Aim: This study was designed to compare Allopurinol (ALLO) and Uric Acid (UA) scavenging activity in a sepsis model.

Materials and methods: Forty male Wistar rats (200–300 g) were included in this study Group 1 (*n* = 10) received ALLO (100 mg/kg/i.p) 3 h prior to septic challenge. Group 2 (*n* = 10) received UA 3 h before septic injury Group 3 consisted of 10 untreated septic animals. Groups 1, 2 and 3 were subjected to i.p. injection of (100 mg/kg) *E. coli* 0111 B4 endotoxin. Additionally 10 rats (Group 4) served as non-septic controls (sham) Six hours after endotoxin animals were killed and liver and lung samples were removed for malondialdehyde (MDA) analysis (thiobarbituric reaction). MDA is a stable end-product of lipid peroxidation. Statistical evaluation using a multiple comparisons procedure was used if ANOVA showed differences among groups.

Results: The mean levels of MDA were significantly elevated among those rats receiving only i.p. endotoxin Treatment with allopurinol and uric acid reduced these MDA values Significantly lower MDA levels were observed among the animals in the uric acid group.

Conclusion: The protection given by uric acid against lipid peroxidation seem greater than those produced by pretreatment with allopurinol

Influence of sepsis on neutrophil CD11b adhesion protein expression

S.A. Delgado, J.A Ferrón, M.L. Delgado, F. Ruiz, A. Collado and A. Mansilla *Virgen de las Nieves Hospital, Unit of Experimental Surgery, Coronel Muñoz Street, 18014 Granada, Spain*

Aim: Neutrophil (PMN) adhesion to endothelium is considered a necessary step for PMN-mediated toxicity. The integrin molecule CD11b/CD18 on the PMN is believed to be important in this process. We hypothesized that sepsis produces an increased neutrophil CD11b expression

Materials and methods: Twenty male Wistar rats weighing approximately 300 g were randomly assigned to the control group (*n* = 10) or to the endotoxin-treated group (*n* = 10) which received the intraperitoneal (i.p.) injection of *E coli* 0111.B4 endotoxin (100 mg/kg). After 6 h of endotoxin administration the rats were anaesthetized and blood samples were collected from inferior vena cava and mixed with 0·8 ml of 3·8 per cent sodium citrate Mean receptor density per PMN was quantified with flow cytometry using a fluorescent-labelled monoclonal antibody (MAS 370) (20 μg/ml) directed against the CD11b receptor. Statistical significance between the control group and treated group was determined with unpaired Student's test *P* < 0·5 was considered significant

The possible role of sepsis on the neutrophil CD11b expression is analysed in this model

Sepsis is associated with an inability to upregulate neutrophil CD16 postoperatively

R.J. Delicata, E.V. Davies, E.J. Pettit and P.D. Carey
Department of Surgery, UWCM, Heath Park, Cardiff, South Wales CF4 4XN, UK

The CD16 receptor expressed by neutrophils (PMN) is attached to the cell membrane by a GPI-link and is readily shed into the circulation where it forms immune complexes which are then destroyed by phagocytosis

CD16 expression was measured in 15 patients [eight males and seven females, mean age 64 years (range 34–80 years)] undergoing elective abdominal surgery PMN were harvested by density gradient on Ficoll-hypaque and labelled with rhodamine-phycoerythrin-conjugated anti-CD16 monoclonal antibody (RPE-CD16 mAb) PMN CD16 expression was determined by flow cytometry and expressed as mean channel fluorescence (mcf) The presence of postoperative sepsis was determined using the criteria outlined by Bone *et al.* Four patients had a septic postoperative event (septic *n* = 4) (non-septic *n* = 11).

	Pre-Op	Day 2	Day 4	Day 5
Septic	2014·5*†	2684†	3283	2483
Non-septic	823*‡	3551‡	3823	1033

**P* < 0 001 (Mann-Whitney *U*-test); †*P* = n s , ‡*P* < 0·01 (Values = median mcf)

Postoperative sepsis is associated with higher preoperative PMN CD16 expression but septic patients are unable to upregulate this expression postoperatively in contrast to non-septic patients. This receptor over-expression may be due to a defect in CD16 production resulting in decreased immune complex formation. Phagocytes are then unable to deal with non-complexed foreign protein leading to enhanced sepsis.

Inhibition of arachidonic acid metabolism may mediate the cyclosporin A effect on human pulmonary macrophages

J. Arias-Diaz*, N. Villa†, J. Hernández*, C. García*, A. Cuadrado*, E. Vara† and J.L. Balibrea* *Departments of *Surgery, Hospital San Carlos, and †Biochemistry, Faculty of Medicine, Universidad Complutense, Madrid, Spain*

Both cGMP and arachidonic acid (AA) metabolites have been implicated in the release of TNF-α by macrophages (Mϕ) We previously found that carbon monoxide (CO), rather than nitric oxide (NO), is responsible for the cGMP increase observed in activated human Mϕ Cyclosporin A (CsA) has been shown to inhibit TNF-α production by Mϕ, and to induce lipid peroxidation (a known endogenous source for CO generation) In this study we investigated the effect of CsA on TNF-α production by human pulmonary Mϕ, and the ability of this molecule to modify AA metabolism and CO generation. Pulmonary interstitial Mϕ were obtained from multiple organ donor lungs by enzymatic digestion. Donors with recent history of tobacco smoking, more than 72 h on mechanical ventilation, or any radiological pulmonary infiltrate were discarded. After 24 h-preculture, purified Mϕ were cultured for 24 h in the presence or absence of LPS (10 μg/ml), LPS + γIFN (100 U/ml), CsA (0·5, 1, 10, and 100 μM), deferoxamine (50 μM), indomethacin (30 μM), and combinations. In some experiments, AA (2 μM) was added 15 min before termination. Phospholipase A_2 activity, prostaglandin E_2 (PGE_2), lipid peroxidases (LPO), and cGMP content of the cells, and TNF-α, PGE_2, CO, and NO release to the medium were determined. In unstimulated Mϕ, CsA produced a dose-dependent increase in LPO, CO (4·01 ± 0·21, CsA 10 μM *vs* 2·60 ± 0·25, control, pmol/μg protein, *n* = 6, *P* < 0·01), and cGMP generation, without modifying TNF-α release. CsA also dose-dependently inhibited the LPS + γIFN-induced TNF-α (4·3 ± 0·3 *vs* 14·7 ± 0·5, pg/μg protein, for CsA 10 μM, *n* = 6, *P* < 0·01) and PGE_2 (3·35 ± 0 13 *vs* 5·37 ± 0·15, pg/μg protein, for CsA 10 μM, *n* = 6, *P* < 0·01) production, while further increasing the LPS + γIFN-induced LPO and cGMP ($0{\cdot}57 \pm 0{\cdot}01$ *vs* $0{\cdot}48 \pm 0{\cdot}01$, pmol/μg protein, for CsA 10 μM, $n = 6$, $P < 0\ 05$) accumulation, and without modifying NO generation Our results suggest that CsA inhibits TNF-α release by human pulmonary Mϕ, and that this effect may be mediated by inhibition of AA metabolism, but not by changes in NO, CO or cGMP production Although PGE$_2$ is usually regarded as an inhibitory stimulus, AA metabolism might act as a permissive factor for the LPS-induced, CO and cGMP-mediated, TNF-α production by these Mϕ.

S-adenosyl-methionine protects human type II pneumocytes against the TNF-α-induced inhibition of surfactant synthesis by mechanisms other than glutathione synthesis

J Arias-Díaz*, N Villa†, P. Ortíz*, J. Calatayud*, C. García-Carreras*, E. Vara† and J L Balibrea* *Departments of *Surgery, Hospital San Carlos, and †Biochemistry, Faculty of Medicine, Universidad Complutense, Madrid, Spain*

TNF-α-induced inhibition of surfactant synthesis seems to participate in the pathogenesis of the adult respiratory distress syndrome In previous studies we found that prostaglandins (PG), nitric oxide (NO) and carbon monoxide (CO) participate in the mediation of the TNF-α effect in type II cells Free oxygen radicals may induce the synthesis of PG, and they have also been implicated in the mediation of the cytokine actions. In this study we investigated whether antagonising oxygen radicals could prevent the effect of TNF-α on type II pneumocytes Multiple organ donors were used as a source of lung tissue Type II pneumocytes were isolated by enzymatic digestion, adherence separation of macrophages, and gradient purification After 24-h preculture, cells were cultured for 24 h in the presence or absence of TNF-α (100 ng/ml), IL-1 (30 U/ml), L-buthionine-sulfoximine (BSO, 0·2 mM), deferoxamine (50 μM), methionine (12 mM), *N*-acetyl-cysteine (12 mM), *S*-adenosyl-L-methionine (SAMe, 12 mM), and combinations. NO and CO release to the medium, and lipid peroxides (LPO), glutathione (GSH), cGMP and PGE$_2$ content of the cells were measured. In a different set of experiments D-(U-^{14}C)glucose was added to the medium and the labelling of several lipid fractions, including phosphatidylcholine (PC) and phosphatidylglycerol, the main surfactant components, was determined D-(U-^{14}C)glucose incorporation into PC was selectively inhibited in the presence of TNF-α or BSO, an inhibitor of GSH synthesis. Both additives also increased baseline LPO, cGMP and PGE$_2$ content, as well as CO and NO release Although the TNF-α-induced increase in LPO was prevented by all antioxidants, only SAMe was able to revert completely the effect of TNF-α on PC synthesis ($4{\cdot}04 \pm 0{\cdot}07$, TNF-α + SAMe, *vs* $1{\cdot}50 \pm 0\ 12$, TNF-α, and $3{\cdot}76 \pm 0{\cdot}11$, control, pmol/μg protein, $n = 9$, $P < 0{\cdot}01$ for TNF-α) Interestingly, this effect of SAMe was apparent even in the presence of BSO ($3{\cdot}84 \pm 0\ 06$ pmol/μg protein, $n = 9$), which, however, was able to revert all changes induced by the other GSH precursors. Our results suggest that the intracellular generation of oxygen radicals may participate, although not as a primary mediator, in the effect of TNF-α on PC synthesis. SAMe protects human type II pneumocytes from the inhibitory effect of TNF-α, and it seems to exert this effect mainly by GSH-independent mechanisms

The effects of vagotomy on bacterial translocation: an experimental study

M. Doganay, N.A. Kama, F.M. Avsar, M. Aksoy and A. Yazgan *4th Department of Surgery, Ankara Numune Hospital, Ankara, Turkey*

Introduction: The effects of truncal vagotomy and proximal vagotomy on bacterial translocation were studied on rats in this experiment.

Materials and methods: The rats were divided into three groups Only oesophageal and gastric manipulations were performed in the control group. The anterior and posterior vagi were found and 0·5–1 cm pieces were taken out in the truncal vagotomy + pyloric dilatation group, in addition pyloric dilatation was performed by Fogarty catheter. The branches of vagi leading to rumen and corpus were first tied by 5/0 silk then resected in the proximal gastric vagotomy group. All animals were killed on day 7. Qualitative and quantitative tissue cultures of caecum, liver, spleen, mesenteric lymph node were taken and a tissue sample from ileum was obtained for histopathological examination on light microscopy

Results: At the end of microbiological study, the bacterical concentration on caecal wall was 10 68 × 108 in truncal vagotomy group while it was 0 53 × 108 in proximal gastric vagotomy group Bacterial translocation was observed more on vagotomy groups than control groups at mesenteric lymph node, liver and spleen Bacterial translocation was more on truncal vagotomy group than proximal gastric vagotomy group ($P < 0{\cdot}05$) Bacterial translocation was observed mostly in the liver, spleen, and mesenteric lymph node at proximal gastric vagotomy group No microorganisms could be cultured on systemic blood cultures Cultures were positive only in one rat in proximal gastric vagotomy group and in two rats in truncal vagotomy group. At the end of the histopathological examination, when histopathological parameteric points given for each rat were calculated, it was $5\ 44 \pm (2\ 12)$ in the truncal vagotomy group and $4\ 77 \pm (2{\cdot}12)$ in the proximal gastric vagotomy group The difference between these two groups was statistically significant ($P < 0{\cdot}05$). Thus there was damage on intestinal wall in the vagotomy groups and it was greater in the truncal vagotomy group than in the proximal gastric vagotomy group.

Comment: It was observed that bacterial translocation could occur after vagotomy. However, it did not cause bacteriaemia. This translocation more frequently occurs after truncal vagotomy than proximal gastric vagotomy

The effects of antibiotics, oxygen free radical scavengers and their combination in the treatment of peritonitis

Ş. Gokgöz, C. Yıldırır, H. Analay, B Dalkılıç and M. Turan *Cumhuriyet University General Hospital, Department of General Surgery, Sivas, Turkey*

The mortality and morbidity rates in surgical patients with abdominal sepsis and infection are still high despite the use of modern surgical techniques and broad spectrum antibiotics. Recent studies indicated that free oxygen radicals, formed after tissue hypoxia, is a factor that causes the mortality rate to remain high by increasing sepsis and tissue trauma. With regard to this idea, it is claimed that in the treatment of such patients, if oxygen free radical scavengers (OFRS) are added, the mortality rates can be decreased Within the scope of these claims, we aimed to investigate whether the combined use of antibiotics with OFRS agents or their use alone achieved a significant difference in treatment and decreased the mortality where intra-abdominal abscess and generalized peritonitis + sepsis developed in rats as a result of iatrogenic perforation of their caecum With this aim 90 rats were separated into six different groups: control imipenem, sulbactam/cefoperazone, OFRS; imipenem + OFRS, sulbactam/cefoperazone + OFRS. Through routine laparotomy on all rats, two holes were made on the front surface of caecum with 23 G needle. By 12 h following surgery, normal saline to control group and drugs according to the groups were injected intraperitoneally. Twelve hours following surgery, three rats taken randomly from each group, were killed and the microbiological culture of the peritoneal liquid was done. In postoperative days 1, 4 and 7, the effectiveness of the treatment was measured by the number of rats survived As a result, we concluded that in the treatment of sepsis, the use of OFRS alone or with the indicated antibiotics in the early postoperative period, did not increase the survival rate.

Some problems of epidemiology, pathogenesis, diagnosis, treatment and prognosis of surgical sepsis

K. Ignatov, D. Stoikov, P. Petrova and U. Petkov *Department of Surgery Medical University of Pleven 1, Svety Kliment Ohridsky Str. 5800 Pleven, Bulgaria*

According to published information sepsis causes the highest mortality (30–45 per cent) amongst surgical and traumatic patients, and is also the most frequent reason for mortality in resuscitation units. According to Wilson, in 55–61 per cent of cases it concerns intra-abdominal sepsis, of which 43 per cent is caused from complications following abdominal surgery. The advancements in resuscitation, microbiology and immunology opened new possibilities for investigating its pathophysiology The aim of the study presented was to do a qualitative estimation of the postoperative septic complications after abdominal surgery and to analyse their structure for an 8-year period (1988–1995). Special attention is paid to 93 cases with intra-abdominal septic shock and multiple organ failure, and the immunological disturbances in some of these patients are emphasized Here are proposed appropriate complex criteria permitting an objective evaluation of the shock severity as well as prognostication of the course and outcome of the treatment on the base of Manncheimer Peritonitis Index (MPI) and Prognosting Peritonitis Index (PPI). The most common reasons for mortality are analysed The experience in the surgical treatment and resuscitation of this group of patients is shared.

Review of micro-organisms eliminated in surgical department and their current susceptibility to antibiotics

J. Jamski, B Polaczek-Kornecka and M. Trystula *III Department of General Surgery, C.M. Jagiellonian University, ul. Prądnicka 37, 31-202 Kraków, Poland*

There is no doubt that widespread use of antibiotics makes, apart from positive therapeutic effects, a sometimes friendly 'environment' for some resistant micro-organisms. Also, antibiotics used in improper doses or combined with different medicines can suppress immunity. Such influence was proved in many previous researches

Analysis of the level of susceptibility of micro-organisms from biological materials, taken from surgical patients, to currently used antibiotics, was the aim of this paper

Continuous changing of bacterial strains' susceptibility to currently used antibiotics demands constant vigilance. Results might be helpful in fighting against infections caused by the most common mirco-organisms, especially in emergency situations, when the antibiotic must be used empirically.

Bacterial strains from such sources as. post-operative wounds, abscesses, leg ulcers, decubital ulcers, from epiglottis or tracheal tubes and intraoperative specimens from peritoneum were taken for analysis. All of them were taken during the last few years From all bacterial cultures we eliminated seven groups of micro-organisms most often responsible for nosocomial infections among our patients. Susceptibility to the recently and the most commonly used antibiotics were stated using antibiotic discs and Miller-Hinton's culture medium. The level of susceptibility was estimated in accordance to commonly accepted gauges We noticed especially high susceptibility of *Staphylococcus aureus* K(+) cultures to amoxycillin with clavulenic acid (Augmentin).

Does bowel preparation enhance bacterial translocation in humans?

I.T. Kale, A Tekeli*, M. Cete, A. Tanık, M. Aksoy* and M A Kuzu *Department of Surgery, Ankara Numune Hospital, *Department of Microbiology, University of Ankara, Turkey*

Prospective randomized studies have shown that bowel preparation adversely affects the infectious complications following colonic resections However, little is known about the effects of bacterial translocation (BT) on these infectious complications. The aim of this prospective study is to assess the effects of bowel preparation on BT A total 47 patients [mean age 46 0 (16–69) years] undergoing elective abdominal operations were studied in four groups, a control (group I, $n = 12$), a mechanical (group II, $n = 10$); a Nichols (group III, $n = 12$) and polyethylene glycol (group IV, $n = 14$) bowel preparation groups Peritoneal swab, ileo-caecal and epi/pericolic mesenteric lymph nodes, liver wedge biopsy, portal venous blood and peripheral blood samples were taken for culture The patients were followed up for postoperative infectious and septic complications. The groups were matched considering age, sex, body surface area and Apache II scores. One in control (8 per cent), two in mechanic (20 per cent), one in Nichols (8 per cent) and three in polyethylene glycol bowel preparation group (21 per cent) demonstrated BT. Infectious complications were detected in one patient with BT in the control group and one in the polyethylene glycol groups.

The preliminary results of this study showed that bowel preparation may enhance BT, but its clinical significance remains unclear.

Management of solitary splenic abscess

I.D. Karanikas, D. Kakoulidis, P. Theodossiou and S. Dendrinos *2nd Surgical Department, General Hospital of Athens, Greece*

Solitary pyogenic splenic abscess remains an uncommon condition and carries a high mortality. The aim of this study is to present three cases of splenic abscess that we had the opportunity to deal with, during a 10-year period, and to illustrate the important factors in aetiology, presentation, diagnosis and treatment. The patients were two males and one female aged 68, 57 and 63 years. Symptoms, initial clinical and laboratory findings included fever, left upper quadrant pain, tenderness, and leukocytosis in all patients, anaemia in one, splenomegaly in two, left pleural effusion in one, and abnormal X-ray in one patient. CT-scanning was diagnostic in two cases while in one it failed to demonstrate the disease which was identified intraoperatively The predisposing factors were splenic infarct, history of trauma, and pancreatitis. All three patients were treated surgically and underwent splenectomy within 3 days after admission There were no deaths, the postoperative course was uneventful and the patients were discharged home between postoperative days 8 and 10. In conclusion early diagnosis and treatment are the key factors for a favourable outcome in patients with solitary splenic abscess. The use of CT- or US-guided drainage has been reported to provide an alternative less invasive and successful management in carefully selected patients However splenectomy and appropriate antibiotics remain the traditional and very effective treatment of splenic abscess

Liver and renal functional and histopathological response in endotoxaemic rats with experimental glutathione depletion

M. Koç*, B. Bozkurt*, F. Coşkun*, O. Cengiz*, E. Demirpençe‡, K Kılınç‡ and F. Aksoy† **Numune Hospital, 2nd General Surgery Clinic and †Department of Pathology, ‡Hacettepe University, Faculty of Medicine Department of Biochemistry Ankara, Turkey*

Endotoxaemia causes tissue ischaemia due to serious blood circulation disorders and triggers free radical generation. Through their chemoattractant effect, free radicals stimulate PMN leukocyte infiltration which in turn causes secondary injury. In preventing tissues from the free radical injury, glutathione (GSH) is a major endogenous antioxidant In this study using dielhylmaleate (DEM), we produced various levels of glutathione depletion in rats which were subjected to endotoxaemia 2 h later (*E coli* O26:B6 endotoxin was used). The rats were killed after 24 h of endotoxaemia and the kidneys and livers were excised. Biochemical observations are done in two stages Firstly, serum SGOT, SGPT, ALP, LDH, GGT, total bilirubin and direct bilirubin between groups and individuals are statistically compared and evaluated before and after medication. Secondly, oxidative injury was evaluated by measuring total and reduced GSH, lipid peroxidation, lactate, hypoxanthine levels and myeloperoxidase (MPO) activities. The results were compared with both sham and endotoxaemic control groups In the GSH-depleted groups, lipid peroxidation levels, MPO activities were significantly higher than both of the other groups. Interestingly lactate levels were high in the endotoxaemia group but low in the GSH depleted groups Also kidneys and livers were examined histologically. Histopathological examination showed that pronounced injury in the kidneys and livers of the endotoxaemia group compared to the sham group and the injury was even more prominent in the GSH depleted groups. All our conclusions suggest that PMN infiltration at least partially contributes to this situation and that GSH has a protective effect against injury. In this study, importance of glutathione for the maintenance of cellular integrity and metabolism were proved by the supporting pathological and biochemical results.

Causes, clinical features, and results of treatment of 14 patients with necrotizing sort-tissue infections

P. Krastanov, J. Losanoff, K. Kjossev, I. Iliev, P. Mitev and V. Mutaftchijski *Department of General Surgery, Military Medical Academy, Sofia, Bulgaria*

Necrotizing soft-tissue infections (NSTIs) are uncommon, although not rare, disease entities that are associated with systemic toxicity, a fulminant course, and a high mortality rate and usually involve one or more of the soft-tissue layers. Primary or idiopathic necrotizing fasciitis is characterized by the absence of an external portal of entry for bacteria.

In an effort to evaluate causes, clinical and microbiological features, and to determine results of treatment, a retrospective analysis was carried out on 14 consecutive patients with NSTIs treated between 1991 and 1995 There were 10 men and three women, who ranged in age from 22 to 76 years. Among them 28·5 per cent (n = 4) initially presented as a primary necrotizing fasciitis. Six patients were identified with NSTIs secondary to postoperative wound complications. In two cases anaerobic streptococcal myositis developed in a course of chronic pilonidal sinus disease Another two patients presented with Fournier's gangrene Bacterial growth was noted in all of specimens from patients on admission, polymicrobial nature of the NSTIs was noted in 71·4 per cent (n = 10) All the patients were treated surgically. Repeated operative debridements were performed, as needed (mean of 4·2/patient) Broad spectrum antibiotic therapy was combined with hyperbaric oxygenation (HBO) in six instances. The overall mortality was 28·5 per cent (n = 4). Plastic reconstruction of the affected area was performed in five patients It is suggested that early diagnosis, aggressive approach to surgical treatment combined with broad spectrum antibiotics and HBO, are required to reduce the inappropriately high mortality rate

Unexpected effectiveness of transdermal nitroglycerin in burns

G. Lupescu Jr.*, G. Lupescu*, C. Giubelan†, I. Velcea† and M. Giubelan† **Department of Cardiology and †Department of Surgery, Tg. Jiu Hospital, TG. JIU, Romania*

Background: Acting directly on the vascular smooth muscle, transdermal nitroglycerin (NG) induces not only general vasodilator effects, favourable in cardiac diseases, but also predominantly local effects The local vasodilation increases the oxygen supply and accelerates the elimination of catabolites responsible for pain and inflammatory phenomena. The predominant decrease of venous pressure facilitates the resorption of interstitial oedema and prevents the plasma extravation. We have found that local transdermal administration of NG, in low concentration (0·05 per cent) thus permitting wide application on the affected region, could induce unexpected beneficial effects in burns.
Aim: Owing to the fundamental role of the circulatory factor in the clinical evolution of the burns, we have investigated the local effects of transdermal 0·05 per cent NG ointment in patients with second degree burns.
Method: Our study was carried out on 48 patients (33 men and 15 women, aged 18–45 years), in a randomized method. Twenty-four patients (Group A) received local 0·05 NG ointment alone and the other 24 patients (Group B) received local usual ointments with cortisone and antibiotics. The area of the burns was approximately equal in the two groups, but no more than 30 per cent. The general treatment and the primary toilet was also identical.
Results: The demarcation between the burns and the living tissues was made up more rapidly in Group A (24–36 h) in comparison with Group B (48–72 h). After 48 h from the beginning of the treatment, 50 per cent reduction in pain was seen in Group A compared to Group B The local bacterial overinfection with resistant germs occurred in 7 per cent of Group A and in 10 per cent of Group B. The period of healing was shorter in Group A (9–10 days) in comparison with Group B (12–14 days) The functional and aesthetical residual problems were 30 per cent and 50 per cent, respectively.
Conclusion: Up to now, NG has been almost exclusively used (excepting Raynaud's disease) for its general effects, even when it was administered transdermally The local effects of NG in burns are frequently quite spectacular and therefore, transdermal NG can be successfully used in surgery.

Percutaneous drainage of abdominal collections guided by ultrasonography

A. Mansilla, A. Albert, R. Fuentes, A. Flores, A. Astruc, R. Fernández, R. Granda and A. López *Hospital 'San Juan de la Cruz', Carretera de Linares s/n. 23400 Ubeda, (Jaén), Spain*

Introduction: Percutaneous catheter drainage of abdominal collections (AC) is a safe alternative technique to surgical drainage We reviewed our experience with this conservative procedure in the treatment of this pathology
Materials and methods: We have evaluated 10 patients (eight men and two women, average age 56·4 years) with the following pathologies and surgical procedures: three necrotic pancreatitis (treated by surgical lavage and drainage of the pancreatic bed), two gastric cancers (two total gastrectomies), one colonic cancer (subtotal colectomy), one cholelithiasis (cholecystectomy), one hepatic cyst (internal marsupialization), one uterine tumour (hysterectomy with bilateral salpingo-oophorectomy) and one giant retroperitoneal lymphoma (resection). In the postoperative period AC were suspected by the presence of fever and abdominal pain and were diagnosed by ultrasonography and TC All the AC were treated by drainage guided by ultrasonography.
Results: Twelve AC were treated (one intrahepatic and eight intra-abdominal abscesses, two intra-abdominal serous collections and one retroperitoneal haematoma). Two patients were drained twice (one gastrectomy and one pancreatitis). Failure occurred in two patients for whom surgical drainage was required (pancreatitis) and one died. There were no complications from the procedure The mean duration of drainage was 8·3 days (range 4–13 days)
Conclusions: Percutaneous drainage of AC is safe and prevents the laparotomy drainage in the majority of cases and it is very well tolerated

Surgical therapy of decubitus ulcers for the disabled patient

P. Metrikas and V. Biskys *Rehabilitation Hospital of Palanga, Vytauto str. 153, 5720 Palanga, Lithuania*

Pressure sores appear in about one-third of all patients with spinal cord lesions The treatment of these is quite long and difficult and sometimes unsuccessful The conservative therapy of the decubitus ulcers is the general trend of cure until now in Lithuania. In September of 1994 we started treating IV–V stages (according to Daniel) pressure sores in patients with spinal cord lesions

This study is based on 15 patients suffering from 25 IV–V stage decubitus ulcers that were operated on The locations of them were 10 ischial region, seven trochanter pressure sores, seven over the sacrum and one pressure sore was on processus spinosus projection below Th12. The decubitus ulcers with severe inflammation reaction around or necrosis inside them were for some time treated conservatively or debridements were performed as the first step of operative treatment The resection of infected bone causing pressure inside was necessary The different flaps or local tissue were used as final way of surgical therapy Twenty-four decubitus ulcers were healed. Marginal necrosis into six flaps and one haematoma under a flap developed postoperatively. Only one ulcer located on processus spinosus below Th12 recurred in week 5 after operation.

The examination findings of seven out of 15 patients between 5 and 16 months after surgery were good. They are changing the usual method of treatment of decubitus ulcers in Lithuania

Effects of L-arginine on tissue perfusion in experimental shock

M.A. Delgado Millan, T. Pascual, J.A. Lorente, E. Mon, D. Ayuso, L. Landin, M. Moreno and A. Esteban *Hospital de Getafe, Ctra. Toledo, 11.5, Madrid, Spain*

Introduction: NO is synthesized from the aminoacid L-arginine by a family of enzymes, the nitric oxide synthetase (NOS); it is involved in the pathogenesis of conditions such as septic shock by endotoxin lipopolysaccharides which act through the release of cytokines It is proposed that the inhibition of the inducible nitric oxide synthase (iNOS) requires 4h after the septic stimulus *in vitro* *In vitro* studies indicate that the activity of the constitutive nitric oxide synthase (cNOS) does not depend on the availability of substrate.
Aim: To test the hypothesis that L-arginine produces haemodynamic effects in early phases of the sepsis by the earlier induction of iNOS or by the activation of the cNOS availability.
Material and methods: We studied anaesthetized and mechanically ventilated sheep monitored with an oxymetric pulmonary artery catheter and an intestinal tonometer placed in the jejunum to measure intramucosal pH (pHi). Sepsis was induced by intravenous infusion of live *E coli* ($0{\cdot}5 \times 10^{-5}$ CFU/kg in 30min) Two groups of animals were studied: control ($n = 6$) and septic ($n = 6$) Haemodynamic parameters, arterial and venous blood gases, pHi and serum GOT, LDH, urea, and creatinine concentration were measured during 5h after septic challenge. After the observation period tissue samples from liver, lungs, small intestine, and kidney were obtained
Results: The infusion of *E. coli* induced hypotension, increase in cardiac output and hyperlactataemia L-arginine treatment of septic sheep broke the acute (within 30min) hypotensive response (from 93 ± 18 to 79 ± 9mmHg, and from 103 ± 7 to 102 ± 13mmHg, in the septic and septic + L-arginine groups respectively, $P < 0{\cdot}05$ for the effect of L-arginine), induced a greater hypotension after 4h (reaching 83·8 and 79 ± 10mmHg at 300min in septic and septic + L-arginine groups respectively, $P < 0{\cdot}05$), and attenuated the hyperlactataemia (reaching 5·7 ± 1·1 and 2·8 ± 1·1mmol/l in septic and septic + L-arginine groups respectively, $P < 0{\cdot}019$) associated with the administration of *E. coli*.
Conclusions: (a) Administration of L-arginine is associated with an amelioration of tissue hypoxia, as measured by serum lactate concentration. (b) There are signs of L-arginine utilization in early (within 4h) phases of sepsis. (c) For unknown reasons, L-arginine minimizes the immediate hypotension associated with the septic stimulus.

Relationship between intestinal metabolic changes measured by jejunal intramucosal pH and morphologic abnormalities in experimental sepsis

M.A. Delgado Millan, P. Segoviano, T. Pascual, J.A. Lorente, E. Mon, D. Ayuso, L. Landin, A. Esteban and M. Moreno
Hospital de Getafe, Ctra. Toledo, 11.5, Madrid, Spain

Aim: To study the relationship between systemic haemodynamic organ function and intestinal intramucosal oxygenation changes with morphological abnormalities in sepsis.
Material and methods: We studied anaesthetized and mechanically ventilated sheep monitored with an oxymetric pulmonary artery catheter and an intestinal tonometer was placed in the jejunum to measure intramucosal pH (pHi). Sepsis was induced by intravenous infusion of live *E coli* ($0{\cdot}5 \times 10^{-5}$/kg CFU in 30min) Two groups of animals were studied: control ($n = 6$) and septic ($n = 6$). Haemodynamic parameters, arterial and venous blood gases, pHi and serum GOT, LDH, urea, and creatinine concentration were measured during 5h after septic challenge. After the observation period tissue samples from liver, lungs, small intestine, and kidney were obtained.
Results: Sepsis was associated with (a) mild but significant hypotension and elevation in cardiac output (b) no changes in haemodynamic and gas exchange parameters indicative of systemic or intestinal hypoxia (venoarterial pCO_2 gradient, arteriovenous pH gradient, tonometric arterial pCO_2 gradient), (c) leucopenia and hyperlactataemia, (d) no change in serum GOT, LDH, and urea concentrations, (e) ischaemic intestinal changes.
Conclusions: (a) In the absence of marked systemic haemodynamic changes and biochemical signs of intestinal hypoxia, there are morphological signs indicative of intestinal ischaemia. (b) Despite normal pulmonary and liver function (as measured by conventional, commonly used, biochemical and haemodynamic parameters), there is marked morphological damage in these organs. (c) Ischaemic morphological intestinal change are related to decreases in pHi, but there are no changes in tonometric arterial pCO_2 gradient. We speculate that morphological tissue damage occurs before abnormalities appear in tests commonly used to evaluate organ function.

Necrotizing perineal infections (Fournier's disease): old remedies for an old disease

I.N. Nomikos, P. Notis, G. Doukas, T. Mariolis, H. Theodosopoulou and K. Kiriakou *Department of Surgery, Athens University, Evgenidion Hospital, Athens, Greece*

Background: Perineo-scrotal gangrene (Fournier's disease), a specific type of necrotizing fasciitis, is a rare and potentially fatal clinical entity which is characterized by progressive spread of necrosis in the skin and subcutaneous tissues of perineum combined with severe systemic sepsis.
Material and methods: We analysed retrospectively seven patients with perineoscrotal gangrene, illustrating the various clinical presentations, problems in management and specific approaches to therapy On admission, all patients were evaluated as being in critical condition, having both severe systemic disease and rapidly advancing gangrene. In all but two patients, a factor predisposing to the fulminant progression of perineal gangrene could be found. After haemodynamic stability was achieved and broad spectrum antibiotics were started, aggressive surgical treatment was initiated. This consisted of unroofing of all infected areas and drainage of the pus, debridement of the necrotic tissues and a wide communication of ischiorectal fossae with the scrotum or the space underlying the labia majora and/or the lower abdominal wall.
Results: In all the patients, the infection was originating from the anorectal area and proved to be multimicrobial in nature. A temporary colostomy was performed in only one patient. Six patients survived and were discharged from the hospital. There was one death on postoperative day 5 due to pulmonary embolism (mortality rate 14·2 per cent).
Conclusion: The crucial points in the management of this synergistic type of infection remains the early diagnosis, the wide and repeated surgical debridements and the proper antibiotic therapy.

Embryonal tissues in complex wound treatment

A.G. Osipov, A.A. Alexeyenko and A.A. Slusarev *Medical State University, Donetsk, Ukraine*

Investigations of clinical picture of trophic wounds in 87 patients at age of 27–78 years showed that ecological factors in our region is a main cause of immune deficiency and reduction of reparative processes. The local wound treatment was conducted using embryonic tissue In cases of extensive wound surfaces embryonic cutaneous flaps were used, which in 3–5 days prevented lysis but gave a lot of epithelization insulas and stimulated granulation tissue After special processing of embryonal pancreatic tissue, solutions saturated with proinsulin-growth factor was obtained Application of this solution to the surface of cutaneous flaps, wound surface and intravascular areas stimulated epithalization and adhesion of wound. Thus, embryonal tissues may be used for local treatment of wounds.

Organ dysfunction during infected pancreatic necrosis: role of open packing

P. Padalino, O. Chiara, M. Segala, L. Fatton, C. Ravizzini, M.G. Turconi, M. Vigorelli and G. Tiberio *Istituto di Chirurgia d'Urgenza Università di Milano, IRCCS Ospedale Policlinico, Milan, Italy*

We examine the evolution of organ dysfunction during open packing in patients with severe acute pancreatitis Fourteen patients with severe acute pancreatitis (graded by Atlanta classification) and multiple organ dysfunction (Gons score) were treated with modified open packing (laparostomy and continuous massive lavage). Patients were operated because of septic-toxic deterioration and presence of organ insufficiency. All patients suffered from infected pancreatic necrosis and they all needed ICU Seven patients came from other departments where they were treated for a mean time of 26 days. Daily debridement was performed in ICU until sepsis abated. The mean time of treatment was 49 days. At admission the mean number of organs involved was 1·8 (range 1–4); respiratory failure was the most frequent dysfunction (60 per cent) During the evolution of disease the mean number of dysfunctional organs was 4 (range 2–7); in particular all patients needed respiratory assistance and amine infusion. Five patients (36 per cent) were submitted to continuous venous–venous haemofiltration because of renal failure and fluid overload. During the evolution of pancreatitis failure of central nervous system was present in 67 per cent of patients, liver in 25 per cent, respiratory in 91 per cent, renal in 25 per cent, cardiovascular in 75 per cent, coagulatory in 33 per cent and gastrointestinal in 41 per cent In particular two organs were dysfunctioning in 33 per cent of cases, three organs in 33 per cent, five in 18 per cent, six in 8 per cent and seven in 8 per cent Three patients died but only one in relation to sepsis (mortality rate 21 per cent). Local bleeding and pulmonary aspiration were the other two causes of death No chronic disease is present in survivors; a contemporary resolution of sepsis and organ dysfunction was observed in all patients Despite severity (mean Ranson· 6·1; mean APACHE II 20, mean C-reactive protein. 251·6 mg/l, CT morphological alteration: seven patients presented D and seven E grade sec. Balthazar–Ranson) the observed mortality was 21 per cent lower than the expected, in particular if we consider the number of organs involved. In our experience an aggressive approach with daily debridement and continuous lavage seems to be necessary in order to control the evolution of infected pancreatic necrosis and to reduce mortality rate in particular when organ dysfunctions are present

Effect of thymostimulin on an intra-abdominal sepsis model

J.C. Salinas, R. Sousa, L Larrad, R Cabezalí, J. Torcal, M.P. Remiro, M. Navarro and R. Lozano *Department of Surgery A, University Hospital 'Lozano Blesa', Avda. San Juán Bosco 15, 50009 Zaragoza, Spain*

The aim of this study is to ascertain if thymostimulin is able to improve the cellular immune response in a model of intra-abdominal sepsis.

Methods: Group A: 10 Wistar-Furth (WF) rats underwent caecal ligation and puncture (CLP) aimed at causing an intra-abdominal sepsis (Baker *et al.* 1983), Group B. 10 WF rats underwent CLP plus thymostimulin (TP-1 Serono®), 2 mg/kg/day subcutaneously during a 7-day period, starting on the day of sepsis. CD3 per cent, CD4+ per cent, CD8+ per cent lymphocyte phenotypes, the CD4+/CD8+ ratio and the IL-2 receptor expression were measured in blood, on the preoperative and postoperative days 1, 3 and 7 by flow cytometry Circulating levels of IL-1 and TNF-α were also measured by ELISA. Wilcoxon, Spearman & Mann-Whitney *U*-test were used in statistical analysis

Results: Rats in Group A showed an increase of CD8+ per cent on the postoperative day 3 ($P < 0{\cdot}05$), the CD4+/CD8+ cell ratio decreased from postoperative day 1 to 3 ($P < 0{\cdot}05$) An initial decrease on day 1 ($P < 0{\cdot}05$) followed by an increase on postoperative day 3 ($P < 0{\cdot}05$) with regard to IL-2R And a significant increase of IL-1 levels within the first 24 h ($P < 0{\cdot}01$). On the other hand no significant variations were found in CLP + TP-1 rats B *vs* A significant differences were found with regard to CD4+ per cent (higher on postoperative day 1, $P < 0{\cdot}01$), CD8+ per cent (higher on postoperative day 1; $P < 0{\cdot}05$; and lower on the postoperative day 7, $P < 0{\cdot}05$), CD4+/CD8+ cell ratio (higher on postoperative day 7; $P < 0{\cdot}05$), IL-2R (higher on postoperative day 1; $P < 0{\cdot}05$), IL-1 (lower on postoperative day 1; $P < 0{\cdot}01$; and postoperative day 7, $P < 0{\cdot}05$) and TNF-α (lower on postoperative day 1, $P < 0{\cdot}01$)

Conclusions: (a) IL-1 and TNF-α serum levels were lower in septic rats treated with thymostimulin (b) Thymostimulin improves immune depression induced by sepsis and may be useful in the treatment of intra-abdominal infections.

The positive effects of diphenylhydantoin on wound healing

M Turan, Y. Sarıoğlu, Ş. Gökgoz, C. Yıldırır and B. Aker *Cumhuriyet University General Hospital, Department of General Surgery, Sivas, Turkey*

In our study, we examined the effect of diphenylhydantoin (DPH) on wound healing Forty-two rats were equally divided into two groups, a control group and DPH group Skin incisions of 2·5 cm were performed on the backs and abdomen of the 42 rats While 0·5 ml normal saline was applied on 21 rats of control group, 0·5 ml fenitoine Rubra (Laboratorios Rubia, SA) containing 12·5 mg DPH was applied on the incision lines of 21 DPH group rats A significant increase in the collagen mass, neovascularization, granulation tissue volume and epithelial tissue on the incision lines of DPH group rats were seen with respect to the control group Hydroxyproline was measured from the skin stripes taken on days 6 and 10 after the abdomen incisions. There was a statistically significant increase in hydroxyproline in DPH group compared to saline group On the skin strips taken on day 10 from the abdomen incisions, wound breaking strength was measured. Wound breaking strength was found out to be 17 ± 2 Newton in the DPH group and 12 ± 4 Newton in the normal saline group. With regard to these results, we concluded that the topical application of DPH that is one of the most important anti epileptic drugs has some positive effects on wound recovery

The use of gentamicin-containing collagen sponges in an infected intraperitoneal environment

W. Vaneerdeweg, E. Van Marck, M. Ieven and E. Eyskens *Department of Surgery, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium*

In order to study the usefulness and the behaviour of gentamicin-containing sponges in the treatment of an abdominal infection, an experimental model comparing gentamicin-containing sponges with plain collagen sponges was developed. A caecal perforation 1 cm in length was made in 60 rats and covered by either a plain ($n = 30$) or a gentamicin-containing ($n = 30$) collagen sponge The rats were killed after 3, 6 and 9 days to evaluate macroscopically and microscopically features of infection and to determine the bacterial concentration in the abdominal fluid. A semi-quantitative grading was used. Furthermore the presence or absence of the sponge was noted The gentamicin-containing sponges tended to be more rapidly resorbed than the plain collagen sponges, but this difference was not statistically significant After 3 days all parameters of infection were graded less severe in the gentamicin group and this difference was statistically significant. After 6 and 9 days the difference between both groups was no longer significant

The results of this study prove that the gentamicin-containing sponges can be used in the treatment of intra-abdominal infection and are effective for at least 3 days

Prophylaxis of postoperative complications in patients with bacterial endocarditis in surgical clinic

L. Vinnitsky, K. Bunatian, E. Mironova, V. Ivanov,
E. Akopdjanova and I. Jarygin *National Research Centre of Surgery, Abrikosovsky 2, Moscow, Russia*

The present study was based on 70 patients with acquired valvular disease with or without bacterial endocarditis. Together with traditional treatment (surgical and antibiotic) we used Imunofan (Russia), which is a synthetic hexapeptide with immunomodulatory, anti-inflammatory, and detoxicatory effects in some patients Treatment course was 4–15 i m injections of 1 ml 0·005 per cent Imunofan solution every second day. Preparation was ordered according to the results of the immunological survey which included lymphocyte subpopulations of peripheral blood studied on Laser cytometer FACScan (Becton Dickinson, USA) with 8 McAb (Russia) and neutrophile phagocytic activity (NPhA) studied with latex. Administration criteria for Imunofan were changes in CD4/CD8 ratio (< or >1·4 ± 0·2), decrease of B-lymphocytes (CD22) level (n = 7·3 per cent ± 1·5 per cent) and NPhA (n = 75·4 per cent ± 1·4 per cent). Immune correction was performed pre- or postoperatively. We found a lower number of postoperative complications when using Imunofan before operation. At the same time using Imunofan after operation led to successful postoperative period: reduction of clinical symptoms of bacterial endocarditis Concerning the immunological events, we found restoration of CD4/CD8 ratio, increase of B-lymphocytes (CD22), NPhA and IL-2 receptor (CD25) expression From our clinical and laboratory data we suggest the inclusion of immunomodulatory preparations (such as Imunofan) in complex immuno-rehabilitation programmes for bacterial endocarditis patients, using it pre- or postoperatively

The effect of octreotide acetate on intestinal changes and survival occurring in sepsis

C. Yıldırır, Y. Sarıoğlu, B. Dalkılıç, Ş. Gökgöz, N. Baruk
and M. Can *Cumhuriyet University General Hospital, Department of General Surgery, Sivas, Turkey*

In spite of the progress in the area of antimicrobial treatment and intensive care the mortality of sepsis remains high. The cause of death due to sepsis is multiple organ failure. The reason of this is the leakage of intestinal luminal contents into the blood circulation and the mucosal destruction of intestine. Therefore we have studied intestinal changes and the effect of octreotide acetate in sepsis. Experimental sepsis was produced in 27 rats by caecal ligation and puncture (CLP). Rats were divided into three equal groups; control, sepsis and treatment group. Height of villi was measured as an indicator of mucosal destruction. In comparison to the control group, a prominent shortening of villi, mucosal oedema, shedding of mucosal cells and haemorrhage areas on the mucosal epithelium were observed in the intestines of septic rats. Octreotide acetate decreased the mucosal destruction. Mean villus height measured 26·7 ± 0·7 in the control group, 18·9 ± 1·9 in the sepsis group and 23·5 ± 1·6 in the treatment group. But octreotide acetate did not produce a meaningful difference statistically ($P > 0{\cdot}05$) These changes in the intestine influenced the survival; while the mean survival duration 31·7 ± 3·2 h in the untreated rats with sepsis it was 49·6 ± 5·5 h in the treatment group.

Intestine

Problems in diagnosis and treatment of malignant tumours of the small intestine (MTSI)

N. Angelescu, N. Jitea, D. Cristian, S Voiculescu and C. Mateescu *Coltea Hospital, Surgical Department, Bucharest, Romania*

Aim: The MTSI by their rare frequency and delusive symptoms set many problems of diagnosis and treatment.
Material and methods: Between 1984 and 1994, eight cases of MTSI (seven males and one female, aged between 24 and 53 years) have been operated on in our department, representing 2 per cent of all malignant gastrointestinal tumours. The pain as a result of the obstruction, followed by chronic blood loss with anaemia and perforation (four patients operated on as emergencies), were the most frequent symptoms, the tumours being localized on jejunum (3) and ileum (5) with a diameter of 3–15 cm. Lymphatic (4), hepatic (2) and peritoneal (1) metastasis were present. We performed a wide resection of the bowel and mesentery, including lymph nodes (in four cases with radical intention). Histopathological findings: four adenocarcinomas, three leiomyosarcoma and a lymphoma. Postoperative treatment was selective and consisted of polychemotherapy (PCT) and cobaltotherapy (^{60}CO).
Results: There was no peroperative mortality, and two local recurrences in 6 months. Survival rate for 5 patients was 32 months. At 5 years there were two survivors with leiomyosarcomas and one with adenocarcinoma, and at 7 years, one with leiomyosarcomas and one with adenocarcinoma.
Conclusions: MTSI are rare and present with non-specific symptoms delaying the diagnosis The presence of metastasis shortens the survival. PCT and radiotherapy have little effect Surgery, in the early stages, remains the main method that can offer possibilities for a long survival.

Digestive surgery over 80 years: a retrospective study of 168 patients

S. Berdah, P. Orsoni, N. Linzberger and R Picaud
Department of Digestive Surgery, Hôpital Nord, 13915 Marseille Cedex 20, France

The aim of this retrospective study was to analyse the results of digestive surgery in 168 patients (103 women and 65 men) over 80 years (mean age 85 years, range: 80–96 years), operated consecutively from January 1983 to January 1996. Surgical procedures were divided into: colorectal (53 patients), biliary (36 patients), oesophagogastric (32 patients), hernias (13 patients), other (34 patients)
Results: Sixty-six complications occurred in 60/168 patients (morbidity rate: 36 per cent) which required nine reoperations The postoperative mortality rate was 15 per cent (26/168 patients) The postoperative mortality rates in emergency and elective procedures were respectively 21 per cent (17/81 patients) and 10 per cent (9/87 patients) These results are detailed in Table 1.

	Colorectal* (per cent)	Biliary** (per cent)	Oesogastric** (per cent)	Hernias** (per cent)	Other (per cent)
Mortality rate					
Emergency	4/18 (22)	2/27 (7)	5/10 (50)	2/7 (29)	5/34 (15)
Elective	6/35 (17)	0/9	2/22 (9)	0/6	—
Global	10/53 (19)	2/36 (6)	7/32 (22)	2/13 (15)	5/34 (15)

Comparison between mortality rates in emergency and elective surgery *n s , **$P < 0·05$

Mortality rates were higher in emergency procedures except in colorectal surgery However, the rates of resections were 60 per cent and 94 per cent, respectively, in emergency and elective colorectal surgery Age distributions were the same in the groups of deceased and non-deceased patients Lastly, two preoperative risk factors were found to be strongly associated with postoperative mortality. chronic renal failure ($P = 0·0004$) and cirrhosis ($P = 0·0009$) These results are similar to those of others series[1,2] and confirm that age alone is not a barrier to surgery

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Multiple diaphragmatic relapsing strictures of small bowel: a rare aetiology for intestinal subocclusion

R. Cabezalí, J.C. Salinas, M.V. Lasa, I. Gil, J.M. Miguelena, J. Ortego and R. Lozano *Servicio Cirugía A, H C.U.Z. San Juan Bosco 15, 50009 Zaragoza, Spain*

Aim: This rare entity has been described in less than 2 per cent of patients taking long-term non-steroidal anti-inflammatory drugs (NSAIDs) These drugs may cause large intestinal ulcers, bleeding, strictures and perforation Our aim is to present a unique clinical case of a man who showed this clinico-pathological condition, in the absence of taking NSAIDs.
Methods: A 46-year-old white man was admitted to hospital in 1993 for epigastric colicky abdominal pain of 48 h duration, not radiated, without any significant finding on physical and biochemical examination He reported a history of colicky abdominal pain (2–3 episodes per year) over the previous 25 years, with nausea and abdominal strain, which disappeared after vomiting or defecation Abdominal plain X-ray showed obstructed small bowel. Endoscopy revealed a gastric tumour of 2 cm diameter Barium intestinal study showed several strictures in the jejunum and ileum. Ultrasonography revealed gallbladder stones. Afterwards, a laparotomy was performed
Results: Intraoperatively, six bowel strictures measuring 10 mm diameter and 1 m long were found in the jejunum and ileum A resection of this section was performed, followed by a side-to-side anastomosis Tumorrectomy of the gastric lesion and cholecystectomy were also performed. The histological study reported the same findings as the small bowel diaphragmatic strictures associated to NSAIDs. At postoperative day 8, he was discharged. One year later, the same symptoms recurred. A barium study showed the presence of two new ileal strictures. Afterwards, a second laparotomy was performed, and the lesions were resected followed by enteroplasties
Conclusions: This rare entity should be included among the different causes of intestinal subocclusion, because of its morbidity These patients need close long-term follow-up because of the high risk of relapsing, and therefore the subsequent laparotomies. Further studies are necessary to achieve new insight into factors associated with this entity, and then to identify the risk population

Intestinal tuberculosis: case report

C. Castro, C Santos and M. Fernandes *Surgery Department, Hospital Garcia de Orta, Pragal, 2800 Almada, Portugal*

We report a clinical case of a 62-year-old female, admitted with abdominal pain, bilious vomiting, and constipation. For 4 months previously the patient had colickly abdominal pain on the right iliac fossa, periods of diarrhoea alternating with constipation, and weight loss of 25 kg. On examination the abdomen felt distended and a tender fixed mass was palpable on the right iliac fossa. The laboratory tests and chest radiograph were normal The plain radiograph of the abdomen suggested high intestinal obstruction The subsidiary tests (such as barium enema, colonoscopy and colonic biopsy, abdominopelvic CT scan) suggested Crohn's disease or caecum malignancy. Due to worsening of general condition, surgery was performed. We found an inflammatory ileocaecal mass with multiple dense adhesions, images suggesting carcinomatosis peritonei, and white caseous lymph nodes. When we tried to perform a biopsy, there was spontaneous rupture of a caseating mesenteric lymph node, suggesting the diagnosis of intestinal tuberculosis, that was confirmed by the histopathological findings.

Mesenteric venous infarction (MVI): personal experience

D. Cerbone, P. Esposito, F. Russo, A. Sorge and G. Cerbone
Department of Surgery, University Federico II and Department of Emergency, New Pellegrini Hospital, Naples, Italy

MVI is an infrequent condition, but is associated with high mortality due to the delay in diagnosis Our retrospective study shows. (a) the disease is more frequent than literature normally reports; (b) it is essential to standardize a laboratory radiological method to accelerate the diagnosis; (c) the possibility of conservative or adjuvant medical therapy. From January 1985 to January 1995, 127 patients have been operated on for intestinal infarction. Aetiology was an embolism of SMA in 51 (40·1 per cent), an SMA thrombosis in 11 (8·6 per cent), a non-occlusive ischaemia in 37 (29·2 per cent), and venous thrombosis in 28 (22·1 per cent). In 28 patients with MVI, the interval between the beginning of symptoms and hospitalization was on average 98h, notably higher than the interval for other causes; the time between hospitalization and operation was 5·4h. All patients have had abdominal pain and 24 patients a variable leucocytosis. Twelve patients received ultrasound, in 10 of them, it showed free liquid in the abdomen and, in one of them mesenteric-portal axis thrombosis too. Twenty of 27 patients were operated on, and were treated with anticoagulative therapy after operation: only three died. Many associated diseases were noted, specially hepatopathy (eight cases). Our experience confirms the delay in diagnosis, moreover these patients come to observation when MVI is already advanced. We have noted only one case of trauma just recovered, he presented with a subitaneous abdominal pain diagnosed by TC with contrast: he recovered after the treatment with heparin i.v. for 11 days. Anticoagulative therapy after operation is very important· in the group of patients submitted to this therapy, mortality was lower than 50 per cent and morbidity 77 per cent. We point out that incidence of disease is meaningfully higher than literature has proved, probably because the prolonged survival of hepatopathic patients disposed to MVI. We advise the leaving of adequate intestinal borders apparently uninjured, in case of resection because 60 per cent of infarction relapse is on anastomosis

Surgical gastrointestinal complications in patients with acute intestinal graft vs host-disease

P. Chirletti, R. Caronna, W. Arcese, A.P. Iori, D. Calcaterra, Y. Puce and V. Stipa *Patologia Chirurgica IX, Cattedra di Ematologia I, Università di Roma 'La Sapienza', Rome, Italy*

Aim: To assess the surgical strategy in treating acute abdominal complications caused by GVHD.

Introduction: Acute intestinal GVHD develops in about 30 per cent of patients submitted to allogenic bone marrow transplantation. 10–20 per cent have severe abdominal complications, such as a digestive haemorrhage or perforation. Mortality reaches 30–60 per cent in patients with acute, grade 2–4 GVHD. These complications arise from intestinal GVHD itself or from intestinal infections due to *Candida* or cytomegalovirus (CMV). They pose complex clinical problems because of their subtle onset; rapid progression towards generalized sepsis and the frequent association between intestinal GVHD and immunodeficiency-related infections of the gastrointestinal tract The surgical strategy in treating acute abdominal complications remains controversial.

Material and methods: We studied 36 bone marrow transplant recipients with acute intestinal GVHD (13·5 per cent of the 266 patients who received bone marrow transplants for haematological malignancies). Seven of the 36 patients had severe acute abdomen: four had severe gastrointestinal bleeding and three acute peritonitis. Patients with gastrointestinal bleeding underwent emergency gastroduodenoscopy, one patient received an embolization, one needed emergency surgery for colonic bleeding. Two of the patients with intestinal perforations (one colonic and one ileal) needed emergency surgery.

Results: Emergency endoscopy detected the source of bleeding (stomach) in only one of the four patients. In the others it suggested ileal or colonic bleeding. Two of the three responded to medical therapy. The patient with gastric bleeding resistant to medical therapy who underwent embolization died 48h afterwards because of persisting bleeding. Another patient with repeated episodes of rectal bleeding with ultrasonographic evidence of thickened walls in the distal ileum and right colon, underwent an emergency right hemicolectomy with ileotransverse anastomosis. Of the three patients with peritonitis, one responded to medical treatment; another had an ileal perforation and underwent emergency surgery by ileocaecal resection with side-to-side anastomosis. The patient is still alive 5 years after transplantation The third patient had a total colectomy with ileostomy because of microperforations and necrosis in the caecum and left colon. This patient died from septic shock 72h after surgery Of the seven patients with an acute abdomen, four had positive blood cultures: two yielded CMV and one staphylococcus. All three patients operated on had neutropenia (<500 × mm^3) and one had a severely decreased platelet count (<30,000 × mm^3).

Conclusions: The surgical strategy in treating acute GVHD abdominal complications must consider three salient points. Surgical intervention for haemorrhage is indicated when medical treatment is unsuccessful. The intestinal segment involved must be removed even if this entails extended resections, because an intestinal diversion leaves active foci *in situ* thereby allowing generalized sepsis Severe neutropenia and thrombocytopenia (<10,000 × mm^3) and blood cultures positive for CMV are associated with high morbidity and mortality.

Secondary malignancies of the small bowel

J.E. Hartley*, I.D. Karanikas*, A.P. Walton*, A.W. McDonald†, P.W.R. Lee*, G.S. Duthie* and J.R.T. Monson* **Academic Surgical Unit, The University of Hull, and †Department of Pathology, Castle Hill Hospital, Cottingham, North Humberside, UK*

Non-primary malignancies of the small bowel are rare and present management difficulties. This study aimed to determine the prevalence of small bowel metastases in our region, and to review the clinical presentation, management and outcome of patients presenting with this problem. Review of North Humberside pathology records for the period 1986–1995 identified 25 patients (11 males and 14 females of mean age 70·2 years, range 32–89 years) whose presentation was ascribed to metastases to the small bowel Symptomatology in 14 patients included pain (n = 11), weight loss (n = 5) and vomiting (n = 5) Eleven patients presented as abdominal emergencies with small bowel obstruction (n = 10), or peritonitis (n = 1).

In the majority of cases the primary malignancy was intra-abdominal (n = 21). Presentation after an extra-abdominal primary was less frequent (n = 2). In two patients the primary lesion was not identified. Most frequent sites of the primary malignancy were the stomach (n = 5), pancreas (n = 3), and bladder (n = 3). The median interval time to presentation was 4 months (range 1–13 months) in patients with advanced primary lesions (TNM stages III–IV) and 40 months (range 5–183 months) in those with early (TNM stages I–II) primaries ($P < 0{\cdot}005$). Twenty-three patients underwent laparotomy; during which 18 underwent resection, two a bypass procedure, and one had simple oversew of perforations (in two patients no further action was taken). Two patients were managed non-operatively. All but one patient had evidence of disseminated disease and surgery was considered palliative. The 30-day mortality was 30·4 per cent for postoperative patients and 36 per cent for all patients. Mean survival of all cases was 4·75 months (range 0–28 months); long-term survival (28 months) only being evident after curative surgery. In conclusion, whilst clinically evident metastases to the small bowel are rare they are seldom isolated, and confer a grave prognosis. Patients should be carefully selected for palliative surgery, since their likelihood of survival is poor. Nevertheless, the development of unexplained digestive symptoms in patients with previous intra- or extra-abdominal malignancy should raise the possibility of metastatic involvement of the small bowel, since early diagnosis and radical surgery may improve outcome

Diverticular disease of the small bowel

G. Kouraklis, E. Misiakos, E. Evangelidakis, J. Kakisis, A Papachristodoulou, S. Rossonis, V. Karydakis and G. Karatzas *2nd Department of Propedeutic Surgery, Athens University Medical School, Laiko General Hospital, Athens, Greece*

Diverticula of the small bowel are usually asymptomatic but occasionally can present with serious complications such as infection, haemorrhage, perforation or intestinal obstruction. This is a retrospective review of 11 symptomatic patients with diverticula of the small bowel treated surgically in our Department, from 1974 to 1995. There were six men and five women with an age range of 42 to 80 years (mean age 66 years). Five patients underwent an elective operation for chronic symptoms such as abdominal discomfort and dyspepsia; two of them had concomitant diseases· diaphragmatic hernia, gastroduodenal ulcer. Six patients were operated on urgently due to rupture of the diverticula and associated peritonitis. One had Crohn's disease and another one small bowel lymphoma. At exploration, four patients had a solitary jejunal diverticulum, three patients had multiple jejunal diverticula, one patient had an ileal diverticulum, two had multiple ileal diverticula and one had jejunal diverticulosis with an ileal (ruptured) diverticulum Surgical treatment consisted of resection of the intestinal segment containing the diverticula, followed by end-to-end anastomosis; coexistent diseases were treated at the same time Postoperative complications were: wound infection in three cases and bronchopneumonia in one case. In conclusion, small bowel diverticulosis should be treated surgically in case of refractory symptoms or in case of severe complications.

Endoscopic sealing of gastrointestinal fistulas

V. Lange and T. Souvatzi *Schlosspark-Klinik, Heubnerweg 2, D-14059 Berlin, Germany*

Most fistulas in a surgical department are due to a surgical complication. This condition can be conservatively treated with good results, however it is time-consuming and expensive Our approach to occlude postoperative fistulas by means of endoscopic fibrin-gluing is able to cut short the time of treatment

The occlusion was performed by injecting fibrin-glue through a double lumen catheter into the fistula The intestinal fistula opening was reached by conventional endoscopy or/and by fistuloscopy, which is the endoscopic intervention through the fistular tract. In 10 years 117 patients were treated by fibrin gluing. The overall success rate was 72 per cent (n = 84). From our results we saw that a fistula shorter than 1 cm cannot be occluded Unfavourable conditions for sealing are fistulas with a long history, active Crohn's disease and a location close to the rectum. If the endoscopic intervention is not successful it at least does not make the situation worse; thus the option for a surgical approach is not altered

Surgical management of complicated Crohn's disease

A Louredo, A. Muñoz-Calero, J.I. Escat, A. Alonso Poza, M.L. Fuenmayor, M R. M.-Menno, C. Duque and M. Trinchet *Servicio de Cirugia Gral I, Hospital Gral Universitario Gregorio Marañon, Dr Esquerdo 46, 28007 Madrid, Spain*

Aim: To report our experience in the surgical management of patients with complicated Crohn's disease.

Material and methods: A retrospective study was carried out on 86 patients seen between 1978 and 1995 There were 46 males and 40 females with a mean age of 37 years (17–76 years). The disease was localized to the region of terminal ileum in 65 (75·6 per cent) patients, ileum and colon in 10 (11·6 per cent), colon in six (7 per cent), intestinal in two (2·3 per cent) and anorectal in three (3·4 per cent). The mean time interval from symptoms to surgery was of 47 months (1–240 months) The clinical manifestations were: pain in 76 cases (97 per cent), diarrhoea in 49 (62 per cent), fever in 32 (41 per cent), loss of weight in 31 (39·2 per cent), bleeding in three (3·8 per cent) All patients received corticosteroids, antibiotics and total parenteral nutrition at least one week prior to surgery

Results: Obstruction n = 41 (61 per cent), abscess n = 21 (31 per cent), fistulas n = 25 (29 per cent), stenosis n = 11 (16·4 per cent) and perforation n = 6 (9 per cent) prompted early surgery. Surgical techniques comprised: ileocolectomy in 62 patients (72 per cent), segmental colectomy in 15 (17 per cent), intestinal resection in four (4·6 per cent), diversion colostomy in four (4·6 per cent), bypass in one (1·1 per cent) and fistulostomy in three (3·4 per cent). Fourteen (16·2 per cent) patients developed postoperative complications (fistulas n = 10, abscess n = 9, anastomotic disruption n = 7, and others n = 6) The mortality has been zero At 10 years 47 (51 per cent) presented recurrences of the disease (mean 41 months; range 4–120 months) as evidenced by radiological, endoscopic and isotopic studies Of these, 16 patients have needed surgery and three needed more than one intervention. The remaining patients with recurrences have been managed medically.

Conclusions: In spite of the high incidence of septic complications during flare up, an aggressive approach to patients with total parenteral nutrition, antibiotics and the use of corticosteroids previous to operation, allowed a reduction in postoperative complications as evidenced by an acceptable morbidity and no mortality. Primary anastomosis has been performed in 82 (95 per cent) patients with an incidence of 11 per cent of fistulas.

Computerized system in order to obtain and analyse the enterogram

M.F. Meseguer*, P.M. Poves, J. Silvestre, J.L. Ponce, J.L. Martinez, P. Yunta, M. Borrego and S. Sancho-Fornos *University Hospital 'La Fe', Valencia, Spain*

Introduction: Through the application of a unipolar electrode to the serosa of the small bowel and thanks to a computerized system, we can measure the electrical activity of the small bowel, an enterogram. Through a computerized system, we can record and visualize this type of wave, processing the action potentials to obtain a series of parameters from intestinal motility The system must be flexible to permit the recording of signals over a long period of time, that permit us to investigate the myoelectric shift complexes (MMC). In order to record the spike bursts it is necessary to reach a very high frequency in a short space of time.

Material and methods: Eight silver chloride electrodes are used with a ninth as reference. The electrodes are attached on a disk of Teflon and fixed to the serosa Eight electrodes are joined to the same number of bioelectrics, amplifying the weak signal The signals, already boosted, are digitized through an analogic-digital transducer, a data acquisition card of National Instruments (NB-MIO-16L) The data are stored in a hard disk The signals are processed through high-pass filters of carding 0·1 Hz, and low-pass filters of carding 500 Hz, and another reject-strip filter of 50 Hz Again, the signal is boosted with a gain factor of 1000. Thereupon, the signal is treated through a Fourier transformer obtaining the fundamental frequency from each path separately. For this a high-pass filter is used, called Butterworth rank 10 Thus, in the small bowel, the frequency of the slow wave is 0·28 Hz, letting the spike bursts go by that possess a frequency >10 Hz The following step is to identify the spike bursts of the enterograms, comparing it with the threshold level.

Results: We can analyse each enterogram, having subroutines that calculate the pointer of motility, amplitude of the spike bursts, the length and the square root Based on the data, we can calculate the spread speed of the MMC and the length of each one of the phases, as well as visualize it in the monitor

Conclusions: This method permits recording, storage and rapid and meticulous analysis of all the electrical parameters that translate the motility of the small bowel.

Prognostic factors of recurrence following surgery for ileal and ileocolic Crohn's disease

V. Pareja, E. Martinez-Mas, R. Lopez-Andujar, F. Caro, J. Ortega, J. Segui and S. Sancho-Fornos *Hospital Francesc de Borja, Gandia, Valencia, Hospital La Fe, Valencia, Spain*

The risk of recurrence following surgery for Crohn's disease is very high, and surgeons should be alerted to the influencing factors involved A univariate and multivariate statistical study of the prognostic factors for recurrence was made based upon 107 adults operated on for ileal and ileocolic Crohn's disease. The recurrence and reintervention rates were determined by means of the corresponding Kaplan–Meier survival curves.

The cumulative risk of recurrence after 5, 10 and 15 years was 30 per cent, 49 per cent, and 59 per cent, respectively. Univariate analysis found the variables of poorest prognosis ($P < 0·05$) to be patient age over 18 years at surgery and at symptom onset, a body temperature in the week prior to surgery of over 37°C, a short preoperative course to the disease, hypoproteinaemia of under 6·5 g/dl, a total affected intestinal length of over 45 cm, and small bowel involvement over 45 cm long. Multivariate analysis in turn showed the following variables to possess independent prognostic value: patient age at surgery, body temperature, total bowel length involved, and protein levels.

The results indicate that recurrence in Crohn's disease is frequent after radical resection, and tends to increase with follow-up. Likewise, a number of prognostic factors may influence the incidence of recurrence in Crohn's disease, however these factors seem impossible to modify, because they only show the severity of the disease.

Perioperative blood transfusion and recurrence in Crohn's disease

J.A. Alvarez Perez, R.F. Baldonedo Cernuda and J.I. Jorge Barreiro *General Surgery Service, 'San Agustin' Hospital, c/ Camino de Heros 4, Aviles, Asturias, Spain*

Aim: To assess the validity of the hypothesis that a perioperative blood transfusion has a beneficial effect in preventing or postponing recurrence of Crohn's disease after resection A retrospective analysis was used.
Materials and methods: We reviewed 34 consecutive patients who underwent a first resection of small-bowel Crohn's disease between 1985 and 1994. The patients with colonic involvement were excluded. They all underwent ileocaecal or small-bowel resection for Crohn's disease with removal of all macroscopic disease. Fifteen patients received 1–6 units (mean 2·5 units) of perioperative blood transfusion, and 19 patients did not receive it. No patient had previously been transfused. The preoperative characteristics of the transfused and non-transfused groups were similar. Mean follow-up period was 61·9 months. Length of follow-up was 12–131 months (mean 61·6 months) for non-transfused patients and 12–126 months (mean 71·9 months) for transfused patients. Recurrence of Crohn's disease was defined as postoperative symptoms and signs of Crohn's disease with typical radiological features and biological evidence of acute inflammation, with histological examination of biopsy specimens or resected specimens of bowel when available. Kaplan–Meier life table analysis was used to compare recurrence rates between transfused and non-transfused patients
Results: Thirteen patients (38·2 per cent) had proven recurrence of Crohn's disease, six of whom had not received a perioperative blood transfusion. Recurrence rates were higher in transfused patients, 7/15 (46·6 per cent), compared with non-transfused patients, 6/19 (31·1 per cent), but this difference did not reach statistical significance. Only two patients of the non-transfused group required further resection.
Conclusion: Perioperative blood transfusion does not prevent recurrence in Crohn's disease.

Jejunal neoplasms: a retrospective analysis

M. Duran Poveda*, C. de Ancos Aracil†, D. Rodriguez-Peña*, F. Esteban Collazo*, A. Almeida*, C. Castro* and S. Tamames* **Department of Surgery, †Department of Internal Medicine, Hospital Universitario San Carlos UCM, Madrid, Spain*

The small bowel (SB), represents approximately 75 per cent of the length of the gastrointestinal (GI). Since the SB provides 80 to 90 per cent of surface area of the GI tract, it might be expected to develop most of the neoplasms Primary neoplasms of the small intestine are extremely rare, accounting for only 1–2 per cent of malignant GI neoplasms. Protective mechanisms against SB malignancies may explain the relative scarcity of these tumours.

The aim of this study is to examine the epidemiological and clinical characteristics of the different types of jejunal neoplasms and their treatment. For this reason, we retrospectively reviewed all the patients undergoing laparotomy for suspected jejunal cancer from January 1985 to January 1995 in our hospital. There were six cases including three adenocarcinomas, one leiomyosarcoma, one carcinoid and one unclassified. Symptoms at presentation included GI bleeding with anaemia, varying degrees of intestinal obstruction, abdominal pain and weight loss. Diagnosis required endoscopy and/or barium studies. Computed tomography played a secondary role in some patients All patients underwent radical surgery None received additional radiotherapy or chemotherapy. All patients are alive at the present moment.

Jejunal cancer consists of several types of rare tumours with a very low overall incidence. It is of major importance to recognize these tumours as a possible cause of abdominal symptoms thereby providing early detection and a successful management. Surgery continues to play a primary role in the treatment of these neoplasms.

Intestinal ischaemia caused by venous thrombosis

C. Santos, M Fernandes and J. Giria *Surgery Department, Hospital Garcia de Orta, Pragal, 2800 Almada, Portugal*

Aim: To determine the importance of the evaluation of coagulation tests in the diagnosis of intestinal ischaemia caused by venous thrombosis
Study design: An extensive evaluation of coagulation tests was done in four patients with mesenteric venous thrombosis that was diagnosed after surgical exploration. All cases presented with a segmental intestinal infarction that involved the mid-small intestine The diagnosis of mesenteric venous thrombosis was confirmed by: the presence of mesenteric arteriolar pulsation; palpable superior mesenteric artery pulsations, extrusion of venous thrombi from the divided edges of the mesentery
Results: One case had decreased concentration of protein S. Family study has demonstrated protein S deficiency in a sister, and two daughters of the patient. Two cases presented decreased antithrombin III. One of these patients had been submitted to intestinal resection 6 years before with the diagnosis of intestinal ischaemia.
Conclusion: In spite of the rarity of mesenteric vein thrombosis found in the literature; our limited experience advises that in the presence of this clinical situation the finding of a hypercoagulable state makes it possible to establish a therapeutic protocol that significantly reduces morbility and mortality.

Laparoscopy

Biological costs of the learning curve in laparoscopic cholecystectomy

L. Aldrighetti, M. Giacomelli, M. Paganelli, R. Caterini and G. Ferla *Department of Surgery, Scientific Institute H San Raffaele, University of Milan, Italy*

Aim: To analyse retrospectively the complications of laparoscopic cholecystectomy during the learning period of a single surgical team.

Materials and methods: The case material consists of 400 laparoscopic cholecystectomies (VLC) performed by a single surgical team (operator and two assistants), after training on mechanical models. Laparoscopic cholecystectomy was the approach of choice to all patients referred for benign diseases of the gallbladder (gallstones or benign tumours), except for those cases with common bile duct (CBD) stones unsuitable for endoscopic treatment, who were considered candidates for laparotomy. In the presence of suspicious or proved CBD stones, a preliminary endoscopic retrograde cholangiography (ERCP) with sphincterotomy was performed. When ERCP was performed, the LC was delayed by 24h. For elective LC, prophylaxis with broad-spectrum antibiotics (2g cephazoline preoperatively) was administered. Surgical technique consisted of 12mmHg pneumoperitoneum and four ports, having the operator standing in front of the patient. 'Gasless' technique cases were excluded from the present series. For the purpose of the study, perioperative mortality (at any time within 30 days from surgery), major (sepsis, haemorrhage, damage to any structure, and biliary fistulas) and minor complications (pain for >3 days, respiratory or wound infections without sepsis) were analysed.

Results: Three hundred and ninety-four (98·5 per cent) colecystectomies were successfully performed through laparoscopic approach. Six cases (1·5 per cent) required conversion to laparotomy, due to unclear anatomy in four cases (cholecystoduodenal fistula, sclerosis, and cholecystitis) and due to complications in two cases (damage to the cystic artery and to the transverse colon). Perioperative mortality was 0·2 per cent (one case), secondary to MSOF in postnecrotic cirrhosis Two (0·5 per cent) transections of the CBD were postoperatively recognized, and were treated with a Roux-en-Y hepaticojejunonostomy Biliary fistulas from the hepatic bed of the gallbladder occurred in three cases (0·7 per cent), all patients underwent endoscopic sphincterotomy, which was successful in two cases, while one case required laparoscopy to close the patent duct. One case (0·2 per cent) of uroperitoneum due to bladder puncture in a patient with previous partial cystectomy was conservatively treated with complete recovery The overall incidence of major complications was 2·2 per cent (9/400), while minor complications occurred in 10 per cent of cases (40/400).

Conclusions: The difficulties of the learning curve in laparoscopic cholecystectomy seems to be comparable with the those of laparotomy, and an acceptable price to pay for the benefits associated with this procedure.

Preoperative ERCP and laparoscopic cholecystectomy in treatment of choledocholithiasis

J. Ariceta, C. Miranda, C Zazpe, J Jimenez, E. Balen, J. Herrera and J.M. Lera *General Surgery Department, Hospital de Naverra, Pamplona, Spain,*

Aim: Evaluation of the use of preoperative ERCP (endoscopic retrograde cholagiopancreatograph) combined with laparoscopic cholecystectomy for suspected choledocholithiasis was done and we compared the outcome of this treatment with the traditional approach. We quantify the patients rescued for laparoscopic surgery by discarding or treating choledocholithiasis with ERCP

Patients and methods: From January 1994 to April 1996, 454 cholecystectomies were performed in our service, preoperative ERCP were done in 111 patients. Indications for ERCP were clinical or sonographic abnormalities suspicious of choledocholithiasis Thirty-three patients underwent conventional cholecystectomy and 77 laparoscopic cholecystectomy. In this period, conventional choledochotomy was performed in 84 patients (32 emergencies and 52 programmed surgery)

Outputs: There were no complications with ERCP Mean stay for ERCP and laparoscopic cholecystectomy was 5·19 days, while conventional cholecystectomy was 16·4 days ($P = 0·0001$). Also complications was 4·5 per cent for the laparoscopic cholecystectomy as opposed to 11·4 per cent for conventional cholecystectomies ($P = 0·005$).

Conclusions: The treatment with ERCP and laparoscopic cholecystectomy results in a reduced hospital stay and complications We believe that the best treatment for choledocholithiasis is preoperative ERCP and laparoscopic cholecystectomy

Laparoscopic cholecystectomy in patients over the age of 85 years: 61 cases

C. Barrat, N. Rizk, J.M. Catheline and G. Champault
Hospital Jean Verdier, Department of Surgery, Av du 14 Juillet, 93140 Bondy, France

Laparoscopic cholecystectomy (LC) is the treatment of choice in the management of symptomatic gallstones. Old age was absolute or relative contraindication to LC. We reported 61 cases of LC in patients over the age of 85 years

Patients and methods: In 5 years 712 cholecystectomies have been performed, 685 with a laparoscopic procedure Sixty-one (8·9 per cent) LC were performed in patients aged 85–97 (mean age: 88·4) years Six were ASA I, 16 ASA II, 37 (60·6 per cent) ASA III and 2 ASA IV. LC was performed by the 'French method' with four trocars. Operative cholangiography was performed as routine

Results: Eleven (15·1 per cent) of 73 patients aged 85 years or more were refused LC for cardio-respiratory disease; open cholecystectomy (OC) was performed. One patient was refused surgery Sixty-one had LC. Mean operative time was 110min (45–180min). Operative cholangiography was performed 42 times (69 per cent) Ten (16·3 per cent) conversions were necessary, in five cases for choledocholithiasis. There was no mortality. Morbidity rate was 9·8 per cent (5 cases). Mean hospital stay was 7·4 (3–21) days This result was compared with. (a) results of 21 OC (11 OC and 10 conversions) in patients over the age of 85 years In this group operative time is shorter (96min *vs* 110min; ns), mean hospital stay in longer (13·4 days *vs* 7·4 days); (b) results of 640 LC performed in younger patients (<85 years)· operative time is not significantly different (88 *vs* 91min) but conversion rate (2·7 per cent *vs* 16·3 per cent), mean hospital stay (3·2 *vs* 7·4 days) and morbidity rate (4·2 per cent *vs* 9·8 per cent) were significantly lower in this group

Conclusion: LC is highly recommendable for patients aged 85 years or more if an excellent evaluation of anaesthesia risk is performed. LC must be performed by an experienced surgical team. High rates of conversion for whatever reasons has an effect on results of this group.

Biliary injury and its risk factors during laparoscopic cholecystectomy (LC)

E. Boldo, L. Allende, V. Artigas and X. Rius *Department of General and Digestive Surgery, Hospital Sant Pau, Barcelona, Spain*

Introduction: The aim of this work is to determine the incidence, type, diagnosis and treatment of the laparoscopic biliary injuries (LBI) registered in our centre and establish the attributable risk (AR) for the different laparoscopic biliary injury risk factors referred to in the literature.

Patients and methods: We present a prospective study of 420 LC performed in our centre from 1992 to 1996. Data recorded included incidences during LC, results of intraoperative cholangiography, causes of conversion to laparotomy and postoperative complications. Cases of LBI referred to our centre were included in this series. Laparoscopic biliary lesions were classified using the Strasberg-Soper classification.
Results: The incidence of LBI in our centre was 1·9 per cent (eight cases). We recorded four type A and four type E-1 LBI (Strasberg-Soper) cases One type E-2 and one type E-3 LBI referred to our centre were included in the study. Intraoperative cholangiography had not been performed in any case. Diagnosis of the LBI was done postoperatively in nine cases, where ultrasound and ERCP were the imaging techniques used In one case (type E-1), diagnosis was done intraoperatively by laparoscopic visualization Type A lesions were treated by percutaneous drainage and endoscopic sphincterotomy. Three type E-1 lesions were treated by end-to-end choledocho-choledochal anastomosis. One type E-1 and the E-2 lesion were treated by Roux-en-Y hepato-jejunostomy. Type E-3 LBI was treated by Roux-en-Y portal-jejunostomy. All cases did well. In our series the AR to the different LBI risk factors was: 'local factors (chronic inflammation)', 0·49; 'surgeon with more than 25 LC', 0·002, 'aberrant anatomy', 'operative field bleeding' and 'lesions caused by thermal source', 0·0.
Conclusions: Incidence of LBI in our series was low. We have found that being a trained laparoscopic surgeon (>25 LC) has a greater LBI risk than the one attributable to the 'learning curve'. Simpler lesions may be treated by non-surgical therapy with good results. In our experience, referred LBI were more complex, probably due to the referral nature of these cases and the longer postoperative time spent

Laparoscopic cholecystectomy: value of liver function tests as predictors of choledocholithiasis

M. Bortul and L. Calligaris *Istituto di Clinica Chirurgica Generale e Terapia Chirurgica, Università di Trieste, Ospedale di Cattinara, Trieste, Italy*

Liver function tests are routinely performed in patients undergoing laparoscopic cholecystectomy (LC). A series of 436 consecutive LC was retrospectively reviewed in order to assess the value of liver function tests as indicators of choledocholithiasis. Serum total bilirubin, alkaline phosphatase, γGT, SGPT and SGOT were evaluated. Choledocholithiasis was found in 32 patients (7·3 per cent). It was discovered in 27 cases out of 46 preoperative ERC (58·7 per cent), in two by preoperative i.v cholangiography and in three by intraoperative cholangiography. Univariate (*t*-test, χ^2 test) and multivariate analysis (logistic regression) were performed to evaluate the correlation between liver function tests and choledocholithiasis. High levels of bilirubin, alkaline phosphatase, γGT, SGOT and SGPT were significantly related to the presence of common bile duct stones ($P <$ 0·0001). The multivariate analysis showed that total bilirubin ($P =$ 0·0004) and γGT ($P =$ 0·0001) are independent predictors of choledocholithiasis. The positive predictive value (PPV) for elevated total bilirubin was 20 per cent whereas the negative predictive value (NPV) was 97 6 per cent; for γGT the PPV was 26 per cent and the NPV was 97·7 per cent. An elevation of total bilirubin and γGT had a PPV of 36·3 per cent and a NPV of 98·6 per cent.

Liver function tests are reliable indicators of choledocholithiasis and may be useful in the selection of patients for preoperative ERC and intraoperative cholangiography.

Laparoscopic cardiomyotomy for achalasia with peroperative endoscopic control

A. Méziat-Burdin, M. Bourbon, J. Porcheron and J.G. Balique *Hopital Bellevue, CHU St Etienne, Service de Chirurgie Générale, Bd Pasteur, 42055 Saint Etienne Cedex 2, France*

In oesophageal achalasia intra-operative oesophagoscopy allows the surgeon to check the completeness of the myotomy.

Technique: The patient presented with dysphagia as the main complaint. The diagnostic of achalasia was based on radiographical and manometric criteria. The patient had failed to respond to two pneumatic dilatations of the oesophagus. A myotomy was performed With the patient placed in Trendelenbourg position and the surgeon standing between the legs, a trocar was placed as for hiatal hernia Certain technical details are considered important in laparoscopy for Heller myotomy. For oesophageal achalasia, importance is given to intra-operative oesophagoscopy. At the end of the myotomy, the endoscopy allows the surgeon to check the completeness of the myotomy as well as the integrity of the mucosa. This technique must be performed with care in order to avoid a perforation. Postoperatively the follow-up showed excellent results.

After experience of five cases with laparoscopic cardiomyotomy we found this technique simple, less invasive than open surgery, and it could challenge dilatation as the first treatment of achalasia The peroperative endoscopic control allowed a more complete and efficient myotomy.

Intrathoracic migration of the wrap after laparoscopic Nissen fundoplication

G.B. Cadière, J. Himpens, M. Vertruyen and J. Bruyns
Department of Gastrointestinal Surgery, CHU Saint-Pierre, Brussels, Belgium

Patients: Between May 1991 and June 1995, 251 patients underwent Nissen fundoplication by laparoscopic means in our department. In this group, 12 patients underwent concomitant highly selective vagotomy and 30 patients treated were abroad. This study concerned the remaining 209 patients All patients were recalled for evaluation consisting of upper GI series, oesophago-gastroscopy, oesophageal manometry and 24-h pH-metry, and a detailed questionnaire was completed by them in order to obtain Visick evaluation
Results: Of this group of 209, 119 patients have been evaluated radiologically so far with a mean follow-up time of 31 months. Forty-one patients showed intrathoracic migration (ITM) (37 per cent). In 85 per cent of the cases with documented ITM a hiatal hernia was present preoperatively. In 21 per cent of the cases without ITM (63 out of 78) hiatal hernia was also present preoperatively. Of the 119 patients in whom upper GI series was available, a gastroscopy was performed at a median of 31 months postoperatively in 86 patients: 83 per cent of the patients with documented ITM (24/29) and 93 per cent of the patients without ITM (53/57) showed a normal mucosa (non significant) Of the same group of 119 patients, pH metry is available pre- and postoperatively in 29 patients. Percentage of reflux time went down from 12 per cent to 0·5 per cent in cases of ITM (8/29) and to 1 per cent in cases of non-ITM (21/28). not significant. The number of episodes of reflux exceeding 5 min went down from 2 to none in cases of ITM (7/28) and from six to none in cases of the absence of ITM (21/28). Pre- and postoperative recordings of oesophageal manometry are available in 40 patients. Pressure of the LES went up from 10 mmHg to 20 mmHg in both patient groups with (13/40) and without ITM (without 27/40). Ninety-seven patients out of 119 were available for Visick scoring. A Visick score of 1 or 2 was observed in 85 per cent of the patients with ITM (34/40) and in 84·2 per cent of the patients without ITM (48/57). However, a Visick score of 4 was noted in 10 per cent of the patients with ITM (4/40) and 1·7 per cent of the cases without ITM (1/57). This is statistically highly significant.
Conclusion: In our series, intrathoracic migration of the wrap appears to be a frequent complication after laparoscopic Nissen fundoplication. The presence of a hiatal hernia preoperatively does not predict the occurrence of ITM. The occurrence of postoperative ITM does not influence the efficacy of the anti-reflux mechanism as demonstrated by clinical, gastroscopic, manometric and pH metric means. However, presence of ITM does significantly increase the need for reoperation after laparoscopic Nissen fundoplication.

Is it possible to predict risk of conversion in elective laparoscopic cholecystectomy?

A. Cagnazzo, F. Razzetta, C. Bianchi, E. Varaldo and F.P. Mattioli *Department of Surgery, University of Genova, V. le Benedetto XV, 8 16132 Genova, Italy*

The risk of conversion (CV) during laparoscopic cholecystectomy (LC) has been stated to be around 2–7 per cent by most authors. This risk seems to be dependent on surgeon's experience, presence of complicated disease and on factors related to the patient. The possibility of predicting risk of CV might be useful for informing the patient or for identifying the cases in which LC is not feasible. With this aim we review our experience of 264 consecutive LC. The 264 patients were 32 children (mean age 6·2 years) and 232 adults (mean age 48·9 years). We consider only the adult group. There were 81 men and 151 women. There were 47 patients older than 65 years. Mean duration of symptoms was 10·3 months. No patients showed acute complications of cholelithiasis. Previous abdominal surgery was present in 58 cases and morbid obesity in eight. Statistical analysis of proportions between the group of converted and non-converted patients was performed with χ^2 test, while in case of parametric data Student's t-test was used. CV to open cholecystectomy was necessary in 11 patients (4·16 per cent). The mean age of this group was 62·9 years (($P < 0\cdot05$). Five CV occurred in patients older than 65 years ($P < 0\cdot05$). There were six men and five women (P = n.s.). Six cases belong to the group of the first 50 LC ($P < 0\cdot05$). Five converted patients underwent abdominal surgery before LC (P = n.s.), but only in one case of previous renal aneurysm the operation was the reason of CV. During LC we found pericholecystic adhesions in 36 cases (3 CV), anatomical anomalies in 19 (2 CV), diffuse adhesions in 16 (2 CV) and Mirizzi syndrome in two (both converted). Specific preoperative factors of CV are not present in our experience. Age and duration of symptoms are general predictive risk but are not helpful to characterize a specific group at risk. Sex, obesity and previous surgery do not seem to increase the risk. A careful and patient dissection of the gall bladder allows the successful performance of even difficult LC.

Evaluation of the biliary tree during laparoscopic cholecystectomy: laparoscopic ultrasound *vs* intraoperative cholangiography: a prospective study of 150 cases

J.M. Catheline, N. Rizk, C. Barrat, P. Buenos and G. Champault *Hospital Jean Verdier, Department of Surgery, Av du 14 Juillet, 93140 Bondy, France*

From November 1994 to March 1996, 150 patients treated by laparoscopic cholecystectomy were included in a prospective study, in order to compare intraoperative cholangiography and laparoscopic ultrasound. The biliary tree was successively explored by the two methods in the systematic detection of biliary main duct stones.

The feasability of laparoscopic ultrasound was 100 per cent. Cholangiography was performed only in 125 cases (83 per cent). Time for laparoscopic ultrasound examination was significantly shorter (11·6 *vs* 17·6 min, $P = 0\cdot0001$).

In this study, main biliary duct stones were found in 14 cases (9 per cent). For these detection, results between laparoscopic ultrasound and intraoperative cholangiography were similar. For laparoscopic ultrasound, sensitivity was 80 per cent and specificity 99 per cent; and 78 per cent and 97 per cent for cholangiography. Both examinations together had a 100 per cent sensitivity and specificity.

Laparoscopic ultrasound failed to recognize the intrapancreatic part of the bile duct (25 cases: 17 per cent), did not show anatomical abnormalities detected by cholangiography but did detect unsuspected digestive pathologies. Laparoscopic ultrasound is safe, repeatable and non-invasive. A learning curve is necessary to increase its efficacy. Comparison of cost must be evaluated.

The spilled laparoscopic gallstone

P. Cools, S. Vanderputte, Y. Van der Stighelen and R. Van Hee *University of Antwerp, Department of Surgery, Sint-Vincentiushospital, Antwerp, Belgium*

We report on an intra-abdominal abscess due to a spilled gallstone, 1 year after a laparoscopic cholecystectomy. The patient presented with vague abdominal complaints. Computed tomography revealed an intra-abdominal abscess. During laparotomy a small gallstone was found within the abscess wall. The incidence of intraoperative gallbladder perforation during laparoscopic cholecystectomy and subsequent spillage of bile and stones can be up to 30 per cent. Removal of these stones during laparoscopy is difficult. Moreover, they are thought to gradually dissolve and absorbed. Therefore, most surgeons tend to leave these stones in the abdomen.

Apparently, spillage of bile and stones very seldom causes intra-abdominal infections. In a large study of 77604 patients undergoing laparoscopic cholecystectomy, only three cases of intraperitoneal abscess formation due to spilled stones were found. This case demonstrates that whenever a gallbladder perforation during laparoscopic cholecystectomy occurs, it should be closed with clips or an endoloop to limit spillage of gallstones. Every effort should be made to collect all spilled stones, especially in the presence of infection. Patients presenting with vague abdominal complaints or with an intra-abdominal abscess, even several months or more following laparoscopic cholecystectomy, should be suspected of having stone-related complications.

Manometric calibration for laparoscopic Nissen–Rossetti fundoplication

F. Corcione, M. Maresca, V. Borrelli, V. Cimmino, S. La Manna and A. Scotti *III Department of General Surgery, University Federico II, Via S. Pansini 5, 80131 Naples, Italy*

Our experience in the laparoscopic treatment allowed this approach to perform a Nissen–Rossetti fundoplication for pathological gastro-oesophageal reflux (GER). The same guidelines as in the traditional surgical procedure were applied and intraoperative oesophageal manometry (IEM) was routinely used to calibrate the plication, allowing an objective evaluation of the effectiveness of the technique.

From August 1992 to April 1996 laparoscopic fundoplication was performed in 29 patients, aged from 17 to 65 years, 18 females and 11 males, with symptoms related to pathological GER. In 12 patients, second degree oesophagitis was present, third degree in 15 patients, fourth degree in two patients. Indications for surgical treatment were the unreliability and the high cost of long-term medical therapy in young patients (23 = 79·3 per cent); the persistence of oesophagitis (six = 20·7 per cent) after 6 months of 40 mg/day omeprazole treatment.

The operation was performed with the patient placed in reverse-Trendelenburg, the surgeon's position was between the patient's legs. A 10-mm trocar was introduced, by open technique, 5 cm above the umbilicus in the mid-line for the insertion of a 30° laparoscope and the peritoneal cavity was explored. Four additional ports were used (three 10-mm and one 5-mm cannulas). After the mobilization of the abdominal oesophagus and the exposure of the diaphragmatic crura, a grasper was introduced from the right side to surround the oesophagus posteriorly. Then the anterior wall of the gastric fundus was grasped and easily conveyed up from the back of the oesophagus in order to create a fundoplication according to Nissen–Rossetti. The plication was hypercalibrated (27·6 ± 2·2 mmHg) by IEM.

We had no mortality. A complete regression of the GER-related symptoms was observed postoperatively in all patients. The intestinal motility resumed within 24 h. The mean hospital stay was 2·3 days (range 2–4 days). As to complications, a haematoma, which spontaneously regressed, occurred at the port site. No gas bloat syndrome occurred. No cases of GER relapse were noted at the follow-up (3–45 months). We observed 22 cases (75·9 per cent) of transient dysphagia in the early postoperative period. This however disappeared in most patients within 3 months, in one case (3·4 per cent) dysphagia persisted at 6 months.

In our opinion the 360° Nissen–Rossetti fundoplication is the technique of choice, allowing good functional results thanks to the hypercalibration by IEM. This can avoid the relaxation of the fundoplication, which usually occurs in the postoperative period within 6 months, with consequent GER relapse. On the basis of our experience, laparoscopic treatment of GER appears to be a safe and effective procedure, with results comparable to those following the open technique. Furthermore, advantages related to the minimally invasive approach are to be emphasized

Effects of elective laparoscopic and open surgery on intracellular cytokine production

D. Decker*, C. Lindemann†, K.J. Walgenbach*, P. Decker*, A. Hirner*, F. Bidlingmaier† and A von Rücker†
*Department of Surgery, †Department of Clinical Biochemistry, University of Bonn, Sigmund Freud Str. 25, D-53105 Bonn, Germany

Introduction: Serum concentrations of different cytokines increase after surgical stress But in most studies a marked between-patient variability was observed. To determine the effect of elective surgery on intracellular cytokine production we examined the production of IFN-γ, IL-2 and IL-4 by T-lymphocytes on single cell level after different laparoscopic and open surgical interventions.

Patients and methods: Twenty patients with either laparoscopic ($n = 5$) or open ($n = 5$) cholecystectomies and laparoscopic preperitoneal ($n = 5$) and conventional ($n = 5$) hernia repair were examined. Analysis of intracellular cytokines was performed by three-colour flow cytometry. Blood samples taken before and 2, 24 and 48 h after surgical intervention were compared by the Mann–Whitney/Wilcoxon-signed rank test Differences were considered statistically significant at the $P < 0{\cdot}05$ level

Results: Il-2 is diminished 48 h postoperatively (18·7 ± 3·4 per cent *vs* 12·2 ± 2·2 per cent, $P < 0{\cdot}05$), whereas the production of IL-4 by T-helper cells is unchanged. T-helper cells producing IFN-γ decrease after incision (6·5 ± 1·1 per cent *vs* 9·9 ± 1·9 per cent). The ratios of T-helper cells producing either IL-2 (8:1 *vs* 4·9:1, $P < 0{\cdot}05$) or IFN-γ (3.1 *vs* 1·9:1, $P < 0{\cdot}05$) to T-helper cells producing IL-4 are significantly altered 48 h postoperatively.

Conclusions: Changes of intracellular T-cell cytokine production occur after minor surgical interventions. Measuring alterations of specific T-cell subsets by intracellular staining may help to understand the mechanisms of immune hyporesponsiveness Whether this new method is acceptable for routine observations must be proved in further studies

The incidence of incisional hernia after laparoscopic cholecystectomy

M. Doganay, H. Kulacoglu, N A. Kama, U Gozalan and I. Ziraman *4th Department of Surgery, Ankara Numune Hospital, Ankara, Turkey*

Introduction: Incisional hernias of trocar sites after laparoscopic cholecystectomy have been reported by some centres This study researched the incidence of incisional hernia among laparoscopic cholecystectomy cases

Materials and methods: Laparoscopic cholecystectomy was performed on 438 patients between March 1992 and April 1996 Trocar sites were left open, without any suture closure in all cases Seventy-eight patients who had been operated on at least 1 year ago were included in this study. All patients were examined physically and ultrasonographically in order to determine fascial defects or incisional hernias in trocar sites.

Results: There were 72 female and six male patients with a mean average age 48·2 years. The indication of operation was chronic cholelithiasis in 65 cases and acute cholecystitis in 13 cases. Eleven patients (14·1 per cent) had some systemic disorder Three patients (3·8 per cent) developed wound infection after laparoscopic cholecystectomy. One of these in subumbilical port and other two in sub-xiphoid trocar site. Fourteen patients were found to have a fascial defect (17·9 per cent) (14/78) in physical examination These defects were mostly 10 mm in diameter. In four of the 14 patients the laparoscope was inserted through a supraumbilical incision, whereas 10 patients had a fascial defect in subumbilical trocar sites Another patient who did not have fascial defect in physical examination had a fascial defect which was determined ultrasonographically. Only one patient (1·2 per cent) (1/78) had symptomatic incisional hernia and underwent an elective repair 2 years after laparoscopic cholecystectomy.

Conclusion: It was observed that fascial defects were more frequently seen in subumbilical 10 mm trocar sites (laparoscope), although the incidence of asymptomatic fascial defect was 10·6 per cent (13/78). Symptomatic defect and incisional hernia was seen in only one case, which did not justify the use of fascial closure for trocar sites.

Endoscopic surgery in the elderly

N. Elian, R Wakim, M. Irani and A. Kassasseya *Centre Hospitalier Delafontaine, 93205 Saint Denis, France*

Between 1991 and 1995, 36 elderly patients underwent an endoscopic abdominal procedure. There were seven men and 29 women with a mean age of 85 years (range: 80 to 98 years). The mean ASA score was 2·5. Cholecystectomy was done in 29 patients: 10 had acute cholecystitis including five empyemas, two cholangitis, one gallbladder carcinoma, one secondary pancreatitis and 15 symptomatic uncomplicated gallstones. The other conditions were· three inguinal hernia repairs (one associated with a cholecystectomy), one suture of a perforated duodenal ulcer and three patients had diagnostic laparoscopy (one had an appendiceal abscess surrounded by dense adhesions, one had a strangulated obturator hernia and one peritoneal carcinomatosis with liver secondaries). Conversion to an open procedure was done four times (11 per cent): cholecystoduodenal fistula with surrounding adhesions, appendiceal abscess with adhesions, colonic injury due to the trocar and bowel perforation in a strangulated obturator hernia Average operative time was 61 min (15–130 min). Mean hospital stay was 4 days (1–14 days). All patients were reviewed 1 week and 1 month after discharge Five patients had minor post-laparoscopic complications: one wound haematoma, one wound abscess, one acute urinary retention and two underwent an endoscopic sphincterotomy for choledocholithiasis. Complication rate was 18 per cent. No cardiovascular complications were seen in our series, although 78 per cent of patients had a history of cardiovascular disease The wound complication rate was 6 per cent in our series, it reached 20 per cent for open procedures in elderly patients. The operative time was similar to laparoscopic procedures on younger patients. Two patients died. one of a septic shock secondary to pulmonary infection, and one of an acute pancreatitis complicated by gastrointestinal haemorrhage

Laparoscopy is feasible in elderly patients even with a complicated pathology. Advanced age is not a contraindication for laparoscopy. Operative mortality and morbidity are lower than for open procedures. Consequently, hospital stay is shorter and regaining of patient's prior lifestyle is prompt with few psychological impairments.

Laparoscopic hernia repair: total extraperitoneal approach

M. Ertem, T. Karahasanoğlu, M. Düren, N. Yavuz and S. Erguney *Instanbul University, Cerrahpasa Medical Faculty, Department of General Surgery, Istanbul, Turkey*

Aim: To evaluate the short-term results of laparoscopic hernia repair (LHR) using total extraperitoneal approach (TEP).

Patients and Methods: Twenty-eight patients undergoing 30 LHR using TEP approach have been followed up for a median period of 5 months (3–19 months). There were 26 women and two men with a mean age of 36·1 years Two patients had bilateral disease, five patients had recurrent disease One of the five patients with recurrent disease had already undergone two previous operations with conventional techniques. Nineteen indirect and 11 direct hernias were diagnosed peroperatively. The prosthetic mesh has been laid in all patients around the spermatic cord.

Results: Two patients had early postoperative seroma (7 per cent), in one patient an undiagnosed indirect hernia recurred in early postoperative period (3·5 per cent) On average, patients returned to full daily activities on postoperative day 11.
Conclusion: TEP has to be the method of choice used for groin hernia repair

Method of treatment of calculous cholecystitis complicated with choledocholithiasis

J. Gardovskis, R. Ribenieks, M. Liepins, J. Strods and V. Krumins *Medical Academy of Latvia, Dzirciema Street 17, Riga, LV1007, Latvia*

The aim of present study is to analyse the method of the treatment of gallstone disease complicated with stones in the common bile duct During the period from 1993 till 1996 we have done 1977 laparoscopic cholecystectomies Before the operation ultrasound examination is made. For the patients with stones in the common bile duct or dilated common bile duct in the ultrasound examination or jaundice intravenous cholangiography and ERCP with papillosphincterotomy is done. Preoperative cholangiography was done in 277 cases, in 119 patients we performed ERCP and in 89 cases, when stones in the common bile duct were found, papillosphincterotomy was done In 33 patients after papillosphincterotomy with multiple stones in the common bile duct, control ERCP was performed Residual small stones were found in 43 patients during the first half year after the laparoscopic cholecystectomy All of them were effectively evacuated by ERCP and endoscopic papillosphincterotomy.

Complicated gallstone disease with stones in the common bile duct is effectively treated by ERCP and papillosphincterotomy before or after the laparoscopic operation For the patients with stones more than 1·5 cm diameter in the common bile duct, conventional laparotomy is usually done

Alternatives to CO_2 pneumoperitoneum in laparoscopic surgery: effects on body weight and tumour growth in a rat model

M.C. Giuffrida, N.D Bouvy, L. Tseng, R.L. Marquet, J. Jeekel and H.J. Bonjer *Department of Surgery, University Hospital Rotterdam, Dr Molewaterplein 40, NL-3015 GD Rotterdam, The Netherlands*

Introduction: A controversial issue in laparoscopic colorectal surgery is the treatment of malignant tumours, because of the apparent high incidence of abdominal wall metastasis following laparoscopic resection of colorectal cancer. Earlier studies from our laboratory showed that laparoscopic surgery is associated with less tumour growth than conventional surgery, and, in addition, that insufflation of CO_2 promotes peritoneal tumour growth and is associated with greater abdominal wall metastases than gasless laparoscopy
Purpose: To evaluate the effect of CO_2 on postoperative loss of body weight and tumour growth and whether the use of air pneumoperitoneum or mechanical elevation of the abdominal wall adds to the advantages of minimal access surgery.
Methods: A laparoscopic rat model was used The tumour growth was assessed by the subrenal capsule assay A solid piece of 7–9 mg ROS-1 rat osteosarcoma was implanted underneath the capsule of both kidneys. After 3 days, a small bowel resection was performed laparoscopically, using three different methods to create a working space in the abdominal cavity (CO_2 *vs* air *vs* mechanical elevation of the abdominal wall) Postoperative body weight and tumour growth were determined in both experiments on day 7 Experiment 1: CO_2 pneumoperitoneum and mechanical elevation of the abdominal wall were compared in two groups of rats (19 *vs* 15). Experiment 2 two groups of rats (11 *vs* 11) underwent either CO_2 or air pneumoperitoneum The unpaired Student's t-test and the Mann–Whitney test adjusted for the experiments by stratification were used to analyse data
Results: Experiment 1: there was a significant difference ($P = 0{\cdot}01$) in body weight loss (5·2) between CO_2 group (16·8 ± 1·16) and the gasless group (11·54 ± 2·08) There was no significant difference in tumour growth ($P = 0{\cdot}25$) Experiment 2: Decrease of postoperative body weight was similar after air and CO_2 pneumoperitoneum ($P = 0{\cdot}6$). Tumour growth did not differ significantly after air or CO_2 pneumoperitoneum ($P = 0{\cdot}4$).
Conclusions: Gasless laparoscopy has a beneficial effect on postoperative metabolic consequences, but does not appear to alter oncological consequences comparing with CO_2 laparoscopy Air laparoscopy does not appear to be associated with improved metabolic or oncological consequences.

Vascular injuries of laparoscopic surgery

R. Guloğlu, C. Ertekin, Ş. Dilege, M. Ozgur and M Kurtoğlu *Istanbul Medical Faculty First Aid and Emergency Department, 34390 Çapa, Istanbul, Turkey*

Laparoscopy, being one of the minimally invasive surgical methods, is widely used in general surgery, gynaecology and urology. As in all surgical procedures, complications during laparoscopy occur. However, injury of major vascular structures is a rare (0 05 per cent) but important complication of laparoscopic interventions. It has a high rate of laparotomy and mortality (86 per cent and 8·8 per cent, respectively) In this article, four cases of major vascular injury during laparoscopic cholecystectomy are reported All were due to insertion of the first umbilical trocar. In all four cases laparotomy was immediately performed. Common iliac artery was injured in two patients, aorta in one patient and common iliac artery and vein in one patient. PTFE graft interposition for two common iliac artery injuries, dacron patch reparation for one common iliac artery injury and primary lateral repair for aortic injury and common iliac vein injury were performed. An average of 2·25 units of whole blood were transfused in each case and average stay in hospital was 7 days.

We believe that awareness of major vascular injuries during laparoscopy is the primary factor in preventing them, and in early recognition.

Will laparoscopic herniorraphy become 'the gold standard' in the repair of inguinal hernia?

D. Güzey, R. Kaplan, F. Çelebi, N. Memni, M.A. Gürsoy and E. Arpinar *2nd Department of Surgery, Vakıf Gureba Hospital, TR-34296 Istanbul, Turkey*

For the repair of inguinal hernia, laparoscopic approach is being introduced as an alternative to the traditional methods This procedure is receiving increased popularity Our purpose is to prove the effectiveness of this method in comparison to the traditional methods

One hundred and fifty-nine inguinal hernia patients treated between November 1994 and May 1996, were studied Of those patients, 69 had laparoscopic and 90 had traditional surgery These cases have been evaluated and compared considering their surgery periods, postoperative analgesia requirements/day (A), hospitalization period (days) (B), return to the normal activity (days) (C), return to work (days) (D), recurrence (E), duration of surgery (min) (F), and operation cost ($) (G). TAPP method was applied in laparoscopic approach and Shouldice method was chosen for the traditional ones Four cases of laparoscopic and six cases of traditional surgeries were done for bilateral hernia

The results of this series shows that the patients treated with laparoscopic repair had advantages in postoperative analgesia requirement and in return to normal activity and work, but had disadvantages in duration of operation and cost. In parallel to the development of technology and experience laparoscopy is gaining considerable acceptance in repair of inguinal hernia even though it is not 'the gold standard' as yet

	n	A	B	C	D	E	F	G
Tradi.	90	3–5	7·4	10–15	15–30	1	30–75	550
TAAP	69	0–1	3·5	2–4	7–14	1	40–130	1600

Peritoneal carcinosis following laparoscopic cholecystectomy: case report and literature review

E. Habib, A. Elhadad and M. Mekkaoui *Digestive and Thoracic Surgery Unit, R Ballanger Hospital, Aulnay S/Bois, France*

Subclinical gallbladder cancer (SGC) is a surprising histological diagnosis, and source of reoperation. With laparoscopic cholecystectomy (LC) development, SGC is a source of cancer spread and metastasis.

A 63-year-old woman, with chronic cardiac failure, nephritic syndrome, insulin-dependent diabetes, was operated on laparoscopically for clinical and histological acute cholecystitis 10 months later, she presented with ascites and lower limb oedema. Laparoscopy showed diffuse peritoneal carcinomatsis with ascites Histological analysis found carcinoma from a digestive origin Gallbladder (GB) immunohistochemical analysis with KL1 antibody showed submucosal localization, therefore, peritoneal carcinosis came from GB

This case poses questions of cancer diffusion in SGC after LC, and histological diagnosis difficulties. In a literature review, 23 SGC diagnosed on histological analysis after LC, responsible for secondary regional spread. The patients, women in 80 per cent of the cases, have symptomatic GB lithiasis (9), chronic cholecystitis (9) or acute cholecystitis (5) clinically, and normal GB (3), chronic cholecystitis (11) or acute cholecystitis (8) operatively. In one case there was a doubt about possible GB cancer On histological analysis, serous membrane was invaded (3) and beyond serous membrane invaded (12) in most cases. Reoperation for radical treatment have been done in four patients. Metastases appeared after an average delay of 3 months on gallbladder extraction site port (19), on the other site ports (6), into the peritoneal cavity (8) and in the liver (5) Death (13) occurred after a 6·7-month average delay.

Three SGC after LC are described without secondary metastases at the time of publishing. We did not look for cases in which GB cancer is discovered during LC on operative GB aspect.

Histological diagnostic difficulties are rarely described in sclerosing or chronic cholecystitis. Specific tests as immunology, imprint cytology or others are possible, but selection criteria to use these expensive tests are not well defined. This SGC case is characterized by: primary GB cancer limited to submucosa; GB cancer diagnosis made only after the peritoneal carcinomatsis occurred, 10 months after LC; peritoneal carcinomatsis without port site localization.

Laparoscopic solution of GERD and diaphragm hernia: techniques and economical questions

Z. Hajdu, M. Molnar, Z. Szegedi, I. Furka and I. Mikó
Department of General Surgery, Kenezy Gyula County Hospital, Department of Experimental Surgery, University Medical School of Debrecen, Debrecen, Hungary

Since September 1993 for hiatal hernia and GERD laparoscopic operation has been performed by the authors Their presentation deals with questions concerning the operational techniques.

Both the stapler used in laparoscopic hernioplasty (EndoHernia USSC) and continuous suture were proved to be trustworthy sutures for preparing the wall of stomach The Ethipond and Absolok (Ethicon) sutures are also reliable in the narrowing of the oesophagal hiatus.

A favourable result was accomplished by the well-established technique. Out of 49 operations, 29 were Nissen floppy fundoplications, eight were hiatal hernia operations and the remaining 12 were a combination of both types of operation. There was no postoperatiove morbidity or mortality

Results of laparoscopic vagotomy in the treatment of chronic peptic ulcer disease

T.P. Huttl, G. Meyer, R.A. Hatz and F.W. Schildberg
Department of Surgery, Ludwig-Maximilians-University Munich, Klinikum Großhadern, 81377 Munich, Germany

From October 1991 to April 1996, 14 patients who underwent laparoscopic vagotomy using two different methods were prospectively studied.

Three patients received an anterior seromyotomy with posterior truncal vagotomy (according to Taylor) and 11 patients underwent anterior linear strip gastrectomy with posterior truncal vagotomy (according to Gomez-Ferrer & Taylor). There was no perioperative morbidity or mortality, the actual median follow-up is 22 months (3–52 months). Good to excellent results were found in 13 cases Two patients complained of mild bloating or reflux, one patient who had a simultaneous laparoscopic cholecystectomy had mild diarrhoea up to 6 months postoperatively. No patient suffered recurrence of ulcer, secretory analysis of basal acid output (BAO) and maximum acid output (MAO) showed a 50–70 per cent decrease after vagotomy. Both vagotomy procedures are well suited for a laparoscopic approach, they are effective, easy and safe to perform.

These procedures could be a cost-effective alternative in the treatment of peptic ulcers, especially for the treatment of *H. pylori* eradication failures, gastric hyperacidity without *H. pylori* infection in young patients and for patients with no or reduced compliance or for patients who require long-term use of ulcerogenic drugs.

Laparoscopic repair of perforated duodenal ulcer

S Jianu, F. Costea, B. Martian, R. Mehic, E. Nicolau, R. Stanescu, S. Paun, B. Gaspar and G. Ionescu *Department of Surgery, Emergency Hospital (Spitalul Clinic de Urgenta) Calea Floreasca nr. 8 sectorul 1, Bucharest, Romania*

The study was done to determine the advantages or disadvantages of laparoscopic repair or perforated ulcer. We utilized the method already described, with the patient in the French position, under general anaesthesia. We sutured the perforation with 2-0 Vicryl or 3-0 Mersilk, with intracorporeal knots, in most cases with omentoplasty In 1 year (March 1995 – March 1996) we performed 24 laparoscopic sutures of perforated duodenal ulcers (from a total of 154 operated on in our department). The mean operating time was 90 min. There were three conversions, one for a trocar accident (jejunal wound) and two for adhesions. Oral feeding was permitted on the third day and in-hospital stay was 7 days (range 6–10 days). There was no mortality and no other complications.

The lower rate of complications, shorter hospitalization and quicker return to social life are good reasons for laparoscopic repair of perforated ulcer.

Pulmonary function after open and laparoscopic cholecystectomy

S. Katsaragakis, G. Athanasas, P. Kougias, K. Simeonidis, I. Papadopoulos, E. Mouzakioti and G. Androulakis *4th Surgical Department of Athens University, Fanarioton 3 Street, Pireaus, Greece*

The purpose of this study is to compare the effect of open cholecystectomy (OC) *vs* laparoscopic cholecystectomy (LC) on postoperative pulmonary function.

Sixty patients (30 in each group) who were evenly matched in terms of pulmonary risk factors underwent elective OC or LC. Data from clinical examination, pulmonary function tests and blood gas analysis were determined preoperatively and during the first two postoperative days. Medication requirements were compared.

Compared to the patients who underwent OC those with LC had a lesser degree of reduction in postoperative pulmonary function tests including VC, FVC and FEV-1; and in the impairment of blood gases including O_2 saturation pO_2 and pCO_2. Atelectasis that could be detected in clinical grounds was also less frequent. A 6-fold reduction in the need for pain medication was noted in the LC group

According to our results LC reduces the impairment of postoperative pulmonary function, the need for narcotic analgesics use and the frequency of postoperative complications compared to OC.

Standard laparoscopic cholecystectomy (LAP-SC) and retrograde laparoscopic cholecystectomy (LAP-RC) in the management of acute and chronic cholecystitis

K. Kilakos, N. Paschalides, Ch. Diakaki, S. Tsirigotakis, A Lemoni and A. Rigas *1st Surgical Department, Tzanio General Hospital, Piraeus, Greece*

Laparoscopic Cholecystectomy (LAP-C) is widely used in the management of acute and chronic cholecystitis In standard laparoscopic cholecystectomy (LAP-SC) occasionally there is a need to convert to open In order to avoid that conversion as well as to minimize the postoperative complications we performed another method of laparoscopic cholecystectomy, namely reversed laparoscopic cholecystectomy (LAP-RC).

During the past four years in 1st Surgical Department of Tzanio we performed LAP-C in 476 patients with symptomatic cholelithiasis. Eighty-seven of these patients were suffering from acute or chronic cholecystitis. The group of the 87 patients was divided in two subgroups: Group A including 26 patients underwent LAP-RC, Group B including 61 patients underwent LAP-SC. In the 476 patients LAP-C was converted to open in 3·9 per cent (19/476). In Group A LAP-RC was converted to open in 3·8 per cent (1/26) In Group B LAP-SC was converted to open in 11·4 per cent (7/61) No death was noted and there were no major complications One patient received blood transfusion during the operation because of haemorrhage from the liver bed. Minor complications were seen in 27 per cent (13/476) For the group of the 87 patients the relative numbers were as follows in Group A minor complications were seen in 3·8 per cent (1/26), and in Group B minor complications were seen in 8·1 per cent (13/61)

LAP-C is a reliable method in the management of acute and chronic cholecystitis but has a greater incidence of conversion to open. LAP-RC even if it has difficulties, is an efficient and practical method, it has lower incidence of conversion to open, is accompanied by fewer intraoperative and postoperative complications and provides greater safety in the ligation of the cystic duct and the cystic artery

Is laparoscopic cholecystectomy in acute cholecystitis a safe and feasible procedure?

U.S. Kim, R.J. Delicata, M.K. Roy, N. Warren, B.I. Rees and P.D. Carey *University Department of Surgery, UWCM, Heath Park, Cardiff, CF4 4XN, UK*

The feasibility and safety of laparoscopic cholecystectomy (LC) in acute cholecystitis (AC) has not been previously documented even though LC has become the standard operation for removal of the diseased gallbladder

We performed LC in a prospective series of 40 patients [10 males, 30 females; mean age 54 years (range 28–80 years)] All patients had clinical AC confirmed by radiology (HIDA scan in three patients and ultrasonography in 37). The mean number of episodes of clinical AC prior to surgery was 1 (range 1–2). Nine patients were operated during the acute episode whilst the others underwent elective surgery within 4 months of onset of AC Six patients required preoperative endoscopic cholangiopancreatography for suspected common bile duct stones

LC was possible in 38 patients with two patients requiring conversion due to difficulties encountered whilst dismantling adhesions. The mean operating time was 108 min (range 40–180 min) Peroperative cholangiography was required in seven patients. Drainage of the subhepatic space was required in 17 patients but no postoperative blood transfusions were required. There were no bile duct injuries. The main problem encountered during the procedure was difficulty in grasping the acutely oedematous and distended gallbladder The mean postoperative stay was 2 days (range 1–4 days) and no episodes of upper respiratory tract infection or clinical deep vein thrombosis were observed during the postoperative period.

These findings indicate that LC is possible and safe in the acutely inflamed gallbladder.

Laparoscopic biliary surgery in patients over 75 years old

D. Krawczykowski, N. Passone-Szerzyna and F. Drouard *CH St Charles & CH St Quentin, 59611 Fourmies Cédex, France*

Over a 6-year period (January 1990–December 1995), 85 patients older than 75 years underwent laparoscopic treatment of calculous biliary disease. There were 64 females and 21 males. Mean age was 79·7 (75–96 years) According to the American Society of Anesthesiology, the physical status of those patients was. two I, 32 II, 44 III and seven IV. Among the other risk factors, we have considered the Activity of Daily Living which was correct in all patients except four (one sequaela of a stroke, two disabling arthrosis, one Pickwick syndrome) and the psychological status and the ability to communicate which was fair except in four patients (three depressions and one disorientation)

Laparoscopic procedures were: 75 cholecystectomies, six cholecystostomies, 31 cholangiographies, 17 choledochotomies (seven after a failed or an impossible ERCP), three transcystic choledochoscopies, one cholecysto-duodenal fistula cure, 13 major adhesiolysis

Results: There were three conversions. one bilio-digestive fistula, one choledochotomy and one acute cholecystitis There was no mortality The biliary complication rate was 5·8 per cent· one common bile duct injury which was treated laparoscopically, two biliary fistulas which settled spontaneously, one cholangitis which resolved after Kehr's drain removal and one calculi migration The general morbidity rate was 9·4 per cent one heart failure, one cardiac arrest (resuscitated), two acute respiratory distresses, one sub-hepatic abscess drained percutaneously, two acute confusional states, and one depression Virtually all patients resumed oral feeding and, at least partially, their previous Activity of Daily Living by postoperative day 2. Mean postoperative hospital stay for the 63 discharged patients was 6·5 days (2–23 days).

Conclusions: In older patients laparoscopy seems to improve the outcome of biliary calculous surgery by reducing the postoperative morbidity (15·3 per cent) The minimal disability and the short hospital stay are well known to be of paramount importance in the outcome of senior patients after surgery. Laparoscopy seems therefore an essential tool in the management of biliary calculous disease in the elderly

Postlaparoscopic cholecystectomy syndrome: 'a new problem in the new era'

H. Kulacoglu, N.A Kama, M. Doganay, A Yazgan and I. Ziraman *4th Department of Surgery, Ankara Numune Hospital, Ankara, Turkey*

Introduction: The incidence of postcholecystectomy symptoms has been reported as 20–25 per cent after open cholecystectomy. There have been an increasing number of reports which state some similar and some new problems after laparoscopic cholecystectomy. This study was designed to determine the incidence of postlaparoscopic syndrome

Materials and methods: Laparoscopic cholecystectomy was performed on 438 patients between March 1992 and April 1996 Seventy-eight patients who had been operated on at least 1 year ago were included in this study Detailed histories from all patients following laparoscopic cholecystectomy were recorded Having completed physical examination, alkaline phosphatase, ALT, AST, GGT and bilirubin levels were determined All patients were examined by ultrasonography. Two patients were additionally examined endoscopically for their dyspeptic complaints

Results: There were 72 female and six male patients with a mean average age 48·2 years. The indication of operation was chronic cholelithiasis in 65 cases and acute cholecystitis in 13 cases. Eleven patients (14·1 per cent) had some systemic disorder Three patients (3·8 per cent) developed wound infection after laparoscopic cholecystectomy Nineteen patients (24·3 per cent) had mild symptoms. Nine had epigastric pain, six had flatus and indigestion, whereas four other patients complained of chronic nausea. In 15 cases (23·8 per cent) one or two biochemical parameters was higher than normal levels. Of these patients two had high serum levels before the laparoscopic cholecystectomy as well. No intrahepatic or extrahepatic bile duct anomalies were observed ultrasonographically in any patient. No patient was found to have a long cystic duct remnant.
Conclusion: Totally 15 (23·8 per cent) patients were determined to have postlaparoscopic cholecystectomy symptoms. The incidence is similar to that after open cholecystectomy.

Laparoscopic splenectomy for patients with thalassaemia major: initial experience and results

V. Laopodis, P. Tzardis, E. Kriticos, L. Rizzoti,
A. Papanagnou, E. Vrettou and E. Tierris *1st Surgical Department, Red Cross Hospital, Athens, Greece*

Splenectomy is indicated in patients with thalassaemia major when they develop hypersplenism with a subsequent need for increased transfusions. In spite of the large size of the spleen in such cases, laparoscopic splenectomy was undertaken in eight patients. The procedure was completed laparoscopically in six cases, while in two cases it was converted, due to difficulty to control bleeding from branches of the splenic vein. An effort was made to ligate the splenic artery as an initial step of the procedure, but this was accomplished only in one case. Serial ligations of vessels starting from the lower pole of the organ was carried out in the rest of the patients. The spleen was extracted from the abdomen through a 5-cm incision in the left iliac fossa, which incorporated two port sites. The patients tolerated the procedure very well compared to our experience from the classic open approach and they had a postoperative stay from 3 to 6 days.

From our limited initial experience it seems that laparoscopic splenectomy in the difficult setting of the thalassaemia major patient is feasible but requires extreme care in order to avoid haemorrhagic complications.

Delayed laparoscopy as an adjunct to selective conservative management of liver injury after blunt abdominal trauma: early results reporting on three cases

E. Letessier, F. Genier, O. Armstrong, P. Lasserre, F. Dupas and J.-C. Le Néel *Clinique Chirurgicale A, CHU Hôtel-Dieu, 44035 Nantes Cedex 01, France*

Conservative non-operative monitoring of blunt liver trauma has been advocated forward when the haemodynamic conditions of the patient permits. Laparoscopy today constitutes an approach to the diagnosis of blunt abdominal trauma.
Aim: The aim of this retrospective study was to address the question of delayed laparoscopy usefulness in case of haemodynamically stable blunt liver traumas.
Methods: During a 4-year period, 22 blunt liver traumas, referred to our unit, were haemodynamically stable after initial resuscitation; they were managed non-operatively in an appropriate setting. Delayed surgery was performed in four cases (18·1 per cent): hepatic artery ligation in one case for persistent bleeding, delayed laparoscopy in three cases for intra-abdominal fluid collections (13·6 per cent). Laparoscopic findings were haemoperitoneum without persistent haemorrhage in two cases and intra-abdominal urinary bladder rupture in one case.
Results: In the postoperative course following laparoscopic procedure one patient underwent secondary catheter placement under sonographic guidance for intra-hepatic fluid collection. No patients died We observed no substantial morbidity.
Conclusions: Laparoscopy can assist conservative treatment. Indications of delayed laparoscopy remain rare and it is part of non-aggressive treatment of haemodynamically stable blunt liver trauma victims.

Combinations of subcutaneous abdominal wall lift and optical cannulae to minmize pneumoperitoneum related effects and injuries in laparoscopic surgery

M.M. Lirici, M. Caratozzolo, V. Papaspyropoulos and
L. Angelini *4th Department of General Surgery, University of Rome 'La Sapienza', Policlinico Umberto I, Rome, Italy*

Gasless laparoscopy is indicated in patients with impairment of cardiorespiratory functions, but the exposure achieved with most abdominal lift systems is often poor because of the tenting effect. LaparoTenser® (LT Lucini, Milano, Italy) is a new system for abdominal wall retraction, with specially designed subcutaneous needles (LaparoPlan®), which does not need open laparoscopy, and allows the use of conventional cannulae ensuring minimal tenting effect. To minimize the risk of trocar injuries, the following technique has been employed in 20 cases: after suspension of the abdominal wall, optical trocars (Optic Trocar®, Ethicon EndoSurgery; Visiport®, USSC) are inserted either in the navel area or in the left hypocondrium according to the procedure to be performed, and without any need for Veress needle insertion and CO_2 insufflation, thus improving the safety of the first trocar insertion. Such a technique was employed for laparoscopic procedures of upper or lower abdomen (11 cholecystectomies, five hysterectomies, one ovarectomy, one bilateral hernia repair, one repositioning of inflatable gastric banding, one right colectomy). The preliminary results, analysed in terms of good exposure and safety showed optimal combination of view and easy, clear and safe approach to the abdominal cavity in all but one case This was a case of right colectomy where the exposure of the area of minilaparotomy (right subcostal), needed for specimen retrieval and anastomosis, and the results were very poor. Operation time did not differ significantly from that of conventional laparoscopic operations. Furthermore, to avoid excessive bulging of viscera, frequent when gasless technique is used, LaparoTenser allows combined abdominal wall retraction with low pressure CO_2 insufflation. Combination of subcutaneous abdominal wall lift and use of optical trocars may contribute to improved safety of laparoscopic surgery

Gasless laparoscopic cholecystectomy

M.J. Queirós Medeiros, J. Raposo d'Almeida,
A. Menezes Silva, J.L. Nunes and H. Vasconcelos Dias
Hospital de Pulido Valente, Faculdade de Ciências Médicas de Lisboa, Clínica Universitária de Cirurgia III, Alameda das Linhas de Torres, 117, 1799 Lisboa Codex, Portugal

CO_2 pneumoperitoneum may pose a significant risk for patients undergoing laparoscopic procedures. Gasless laparoscopy, in which abdominal distension is provided by an abdominal wall lifting device, would be an alternative route for patients undergoing surgery of the biliary tree. The purpose of this study was to evaluate whether gasless laparoscopy could be carried out safely. Using this technique, cholecystectomy has been performed in 300 successive patients.

Advantages of the procedure adopted are that, in most cases, surgery can be performed by inserting only three trocars· one umbilical (10 mm), one sub-xiphoid (10 mm) and a third (5 mm) 1 cm below the right costal border in the midclavicular line; sometimes (less than 30 per cent of cases) a fourth trocar (5 mm) is inserted. An airtight pneumoperitoneum is not required; therefore we only use valveless trocars, conventional surgical instruments can be safely and routinely introduced, fogging due to cooling of the optical systems is avoided, high volume irrigation is easily accomplished and continuous aspiration can be applied to the operative site without altering the exposure. The main problem encountered is the difficult exposure of deeply placed hilum, particularly in obese patients, which is solved by using an additional retractor for downward traction of the colon.
Results: Mean duration of surgery (less than 1 h) and hospital stay (2 days) are similar to cholecystectomy performed with CO_2 pneumoperitoneum. The conversion rate to open cholecystectomy was 2·65 per cent. Indications for conversion were: inability to identify the anatomy secondary to inflammatory adhesions or obesity (three cases, 1 per cent), cholecystoduodenal fistula (two cases, 0·66 per cent), bleeding (two cases 0·66 per

cent) and bile duct injury (one case 0·33 per cent). The complication rate was 3·6 per cent, consisting of minor bleeding from the liver or camera port site (three cases, 1 per cent), duodenal injury (one case, 0·33 per cent), bile leakage (four cases, 1·32 per cent) and bile duct injury (one case, 0·33 per cent, diagnosed at the time of surgery and managed by primary repair over a T tube). A second operation was performed in three patients (1 per cent): two for cystic duct leak and one for duodenal perforation. There was no postoperative shoulder pain.

Conclusion: The routine use of gasless laparoscopy is technically feasible, with a low complication rate and early postoperative discharge and is a possible route of choice for cholecystectomy. Mean duration of surgery and hospital stay are similar to cholecystectomy performed with CO_2 pneumoperitoneum and so are the conversion and complication rates. The ability to use conventional instruments reduces the need of disposable instruments making surgery easier and less expensive. This approach obviates complications directly associated with CO_2 pneumoperitoneum. Postoperative shoulder pain is not a common complaint.

Indications and results of laparoscopic splenectomy

G. Meyer, H.M. Schardey, H.G. Rau, R. Schauer and F.W. Schildberg *Department of Surgery, University Hospital Munich Grosshadern, Marchioninistr. 15, D-81377 Munich, Germany*

Splenectomy is a surgical intervention well suited for laparoscopy. It is not difficult to achieve a good exposure of the spleen in the left upper abdomen and the transection of the central splenic vessels is not very demanding. The limiting factor may be the size of the organ and the nature of the underlying disease. Until now we have carried out 22 laparoscopic splenectomies. The indications were various causes of anaemia, splenic tumours, thrombocytopenia and splenomegaly as well as a Moschcowitz–Syndrome and a haemorrhagic splenic cyst each. As single postoperative complication was an infection of the surgical site following splenectomy in the presence of tumour infiltration of the retroperitoneum. The recovery of patients seemed facilitated and shortened in comparison to conventionally operated ones.

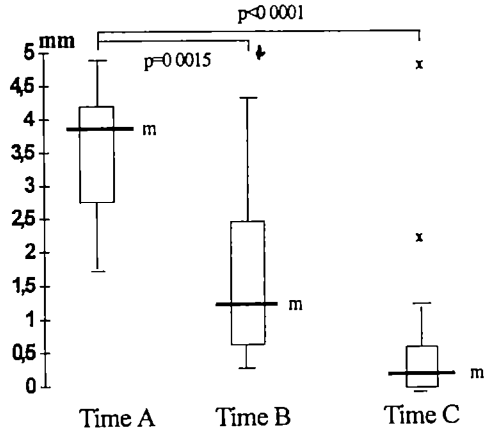
Based on our limited experience we consider laparoscopic splenectomy for benign disease even in the presence of splenomegaly, to be a very good procedure with advantages for the patient. In the case of tumours the indication should be considered individually after careful preoperative diagnostic evaluation.

Chronic abdominal pain: significance of laparoscopy

K. Miller, E. Mayer and E. Moritz *2nd Surgical Department, Landeskrankenanstalten, Mullner Hauptstr. 48, A-5020 Salzburg, Austria*

This study was designed to determine the efficacy of laparoscopy on patients with a history of recurrent and chronic abdominal pain longer than three months, of unknown origin. From September 1990 to May 1994, we performed 66 laparoscopic treatments on 59 patients. The assessment of life quality consist of the disability score, the McGill pain questionnaire, and the visual analogue pain scale, which were completed preoperatively (Time A), then on the day of discharge (Time B), and finally at a mean period follow-up (Time C) of 75·3 weeks. Laparoscopy provided diagnosis on 53 of 59 patients (89·8 per cent). All 66 attempted laparoscopic procedures were completed successfully, no conversion to laparotomy was necessary, and no postoperative complication occurred. Five out of 59 patients (8·5 per cent) revealed no improvement of pain postoperatively, and 6 out of 56 (10·7 per cent) still suffer from pain at the time of the follow-up.

The difference in pain assessment and disability score was statistically significant postoperatively and at the time of the follow-up in relation to the pre-operative score. We believe that laparoscopy is a very useful therapeutic tool in the armamentarium of modern general surgery and should not be confined to diagnostic evaluation only.



pH-metry before and after laparoscopic Nissen repair for gastro-oesophageal reflux disease in 40 patients

S. Msika*, A. Fingerhut*, E. Blezel*, B. Millat*, J.C. Etienne*, P.L. Fagniez*, J.M. Hay* and Associations for Surgical Research† **Hôpital Louis Mourier, 178, Avenue des Renouillers, 92701 Colombes and †8, avenue des Peupliers, 92270 Bois Colombes, France*

The purpose of this prospective multicentric study was to compare results of ambulatory 24-h pH monitoring (pHm) before and after laparoscopic Nissen repair in a large number of patients. Between July 1994 and December 1995, 191 patients (112 males and 79 females) underwent a laparoscopic Nissen repair for gastro-oesophageal reflux disease (GERD). All patients had GERD and/or oesophagitis recurrent or refractory to medical treatment. All patients had preoperative endoscopy and pHm (DeMeester score $n < 15$). Clinical evaluation was performed 1, 6, 12, 18 and 24 months postoperatively. The pHm is performed 6 months and 24 months postoperatively. Mean age of patients was 44·8 years old (21–82 years). The mean duration of operation was 230 min (70–480 min). The mean duration of hospital stay was 4·8 (2–25) days. Actual evaluation could be made on 40 patients who underwent pHm both before and after operation. The mean value of DeMeester score before operation was 65 (normal < 18). This mean value after operation was 18.

We conclude that laparoscopic Nissen repair corrects GERD effectively and should be proposed as the gold standard of treatment.

Laparoscopic Nissen–Rossetti fundoplication: our experience

L. Napolitano, P. Di Sebastiano and P. Innocenti *Scuola di Specializzazione di Chirurgia Generale, Università, G. D'Annunzio Chieti, Casa di Cura Pierangeli, 65124 Pescara, Italy*

Between April 1995 and January 1996 we performed 10 laparoscopic Nissen–Rossetti fundoplications. All patients were suffering from hiatal hernia and gastro-oesophageal reflux disease (GERD) resistant to medical therapy (proton pump inhibitors and prokinetics for 8 weeks at least).

Preoperative assessment included: oesophagogastroduodenoscopy (EGDS) with biopsies, 24-h pH-monitoring; 24-h manometry, contrast oesophagography and DeMeesters symptom scoring. Mean operation time was 150 min, conversion rate was 0 per cent. All patients experienced mild grade dysphagia that resolved spontaneously in 4–8 weeks. Postoperative evaluation was performed in all patients at 12 weeks after the operation. Overall results were characterized by a significant reduction of the symptom score: mean score was reduced from 5·8/9 to 0 2/9. No signs of oesophagitis were seen at control EGDS. 24-h pH-metry demonstrated a significant reduction of the total time at pH < 4, from a mean of 9·05 per cent (6·7–11·4 per cent) preoperatively to a mean of 1·9 per cent (1·7–2·2 per cent) postoperatively and the number of refluxes fell from a mean value of 257 (337–166) preoperatively to 27 (42–20) postoperatively. 24-h oesophageal manometry revealed a rise in lower oesophageal sphincter pressure from a mean of 11 mmHg preoperatively to a mean of 25 mmHg postoperatively.

Our preliminary results demonstrate that laparoscopic Nissen fundoplication is a safe and effective procedure for gastro-oesophageal reflux disease

Does the ultrasonically activated scalpel release viable airborne cancer cells?

C.C. Nduka, N. Poland, M. Kennedy, J.F. Dye and A. Darzi *Academic Surgical Unit, Imperial College School of Medicine at St. Mary's, London, UK*

Viable cancer cells may implant at distant sites and may be a cause of recurrence. One possible mechanism is the inadvertent exfoliation of viable tumour cells during dissection. The ultrasonically-activated scalpel (UAS) utilizes ultrasonic energy to disrupt tissues by cavitation and produces a dense cloud of cellular debris which may contain viable cells. This study aimed at investigating the viability of air-borne cells released during cancer dissection using the UAS and electrosurgery.

Flank tumours ($n = 8$) measuring 1 cm^3 were induced in male WAG rats by subcutaneous injection of 2×10^6 CC531s colon cancer cells. Dissection was performed in cutting mode using the maximum power output of the respective devices Electrosurgery was performed using a standard monopolar electrosurgical unit and a needle probe. Ultrasonic dissection was performed using the Harmonic scalpel using the open surgical handset and the hooked spatula tip. The smoke plume was aspirated using a vacuum pump and bubbled under Hank's balanced salt solution to trap particulate matter. The viability of the cellular material was blindly assessed with the trypan blue test and by *in vitro* culture The morphology of the cellular debris was studied by examination of cytospin preparations.

Large quantities of cellular debris was trapped in the plume from both devices. However, no viable cells were isolated nor did *in vitro* cell growth occur with either device. Examination of the debris from the UAS demonstrated a characteristic mixture of amorphous forms and very few morphologically intact cells The cauterized tumour produced charred cells and tissue fragments.

This study demonstrates that viable air-borne cancer cells are not released following tumour ablation with the UAS or electrosurgery.

Selective preoperative exploration of common bile duct in laparoscopic biliary surgery

P. Orsoni, S. Berdah, N. Linzberger, M. Barthet, J.C. Grimaud and R. Picaud *Department of Digestive Surgery, Hôpital Nord, 13915 Marseille Cedex 20, France*

In patients with symptomatic gallstones, the management of common bile duct stones (CBD) is still controversial. A prospective study was performed of laparoscopic cholecystectomies to determine the place of preoperative exploration of CBD in patients at risk of CBD stones

Patients and methods: Between September 1990 and March 1995, 260 patients with symptomatic gallstones underwent laparoscopic cholecystectomy The indications of exploration of CBD preoperatively were obstructive jaundice, cholangitis, acute pancreatitis, abnormal liver function tests, dilated CBD (more than 7 mm) and eight miscellaneous causes. Exploration was done by endoscopic retrograde cholangiography (ERCP) or echoendoscopy (EE). An endoscopic sphincterotomy (ES) was performed when stones, sludge or pus were found in CBD.

Results: Sixty-eight out of 260 patients (26 per cent) underwent an exploration of the CBD, 27 with EE, and 51 ERCP (10 after suspicion of stone in CBP at EE) We found two choledocholithiasis in four patients with obstructive jaundice, eight out of 10 patients with cholangitis, one out of 10 patients with acute pancreatitis, four out of 29 patients with abnormal liver function tests, and two out of seven patients with dilated CBD. Thirty ES were done on 68 patients (44 per cent), 17 for stones (25 per cent) and 13 for sludge or pus in the CBD (19 per cent). There was no mortality and no morbidity.

Conclusion: The results of the present series suggest that patients with symptomatic gallstones with suspected choledocholithiasis can be managed by preoperative ERCP and laparoscopic cholecystectomy with minimal morbidity and mortality.

Laparoscopic and endoscopic approach to cholecystectomy and choledocholithiasis

G. Palazzini, M. Monti, F.M. Di Matteo, G.P. Bianchini, G. Lippolis, A. Brescia and F. Boccaccini *Third Department of Surgery, University 'La Sapienza' of Rome, Rome, Italy*

We have performed 289 laparoscopic cholecystectomies (LC). We have had no deaths and minimal morbidity with the procedure Three patients had cholelithiasis and common bile duct stones. We recommend endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) with stone extraction as the procedures of choice preoperatively, and postoperatively particularly if choledocholithiasis is diagnosed during LC. We have treated 35 patients with ERCP and the success rate of this technique was about 80 per cent. Complications occurred in nine patients with haemorrhage being the most common. In good hands ERCP with ES and stone removal is an efficacious technique. ES is offered to patients after informing them of the possible complications and the mortality associated with this technique. We adopt the policy of treating choledocholithiasis with ERCP and ES 48–72 h before LC when common-duct stones are discovered preoperatively. Only in two cases have we performed ERCP postoperatively but we have met several difficulties due to local inflammatory postoperative conditions.

We believe that preoperative ES and subsequent LC could be performed with a low morbidity and mortality.

Successful laparoscopic treatment of large abdominal liquoral pseudocyst

R. Macarone Palmieri, B. Benini, R. Bertolini, †A. Massari and †F. Chiappetta *U.O. di Chirurgia Generale 'G. Flajani', U.O. di Neurochirurgia 'G.M. Lancisi', Ospedale S Camillo de Lellis, Rome, Italy*

Abdominal liquoral pseudocyst (ALPC) is an uncommon complication following ventriculoperitoneal shunt (VPS) for non-communicating hydrocephalus. ALPC is due to the irritant action of the cerebrospinal fluid on the peritoneum. ALPC are usually treated by unroofing of the pseudocyst wall via open laparotomy. Aim of this report is to present a case of ALPC successfully managed laparoscopically A 27-year-old man, suffering from a non-communicating hydrocephalus, experienced recurrent malfunction of VPS and was admitted on 20 July 1995 to the Ospedale S. Camillo de Lellis in Rome for persistent headache associated to vomiting and abdominal colicky pain. A tender mass, which occupied the left abdomen, was found on physical examination; a CT scan revealed acute hydrocephalus and confirmed the presence of a large (27 cm diameter) abdominal mass displacing the left colon laterally, the small bowel to the right, anteriorly and superiorly. On 22 July 1995 the patient was operated on by two teams: neurosurgeons removed the malfunctioning ventricular catheter and created a new ventriculo-atrial shunt, meanwhile laparoscopic surgeons performed extended adhesiolysis, wide fenestration and partial excision of the ALPC wall, removal of peritoneal catheter. The postoperative period was uneventful and the patient was discharged on Day 5. Ten months later the patient is asymptomatic. A CT scan shows maintenance of ventriculo-atrial shunt function and complete disappearance of the ALPC In conclusion, it has been shown that laparoscopic approach in the treatment of ALPC must be considered feasible, effective and safe To the best of our knowledge, this is the first case report of laparoscopic management of ALPC.

Complications of laparoscopic cholecystectomy results of a French retrospective survey of 6435 cases

R. Petroni, B. Dousset, M.J Boudet, P.L Fagniez, J.M. Hay* and French Association for Surgical Research (ARC) *Hôpital Louis Mourier, S.ce de Chirurgie, 178, rue de Renouillier, 92701 Colombes, France*

Aim: Evaluation of type and rate of complications after laparoscopic cholecystectomy (LC), treatment and outcome of patients.
Methods: A retrospective and anonymous survey of 6435 LC performed on from 1989 to 1994, in 26 centres by 90 surgeons was carried out. Any cause of patient's death or reintervention, retained common bile duct (CBD) stones and any technical cause of conversion to open cholecystectomy (OC) (except for gallbladder perforations and dissection difficulties) were defined as complications.
Results: The median number of LC for a single centre was 214 (range 29–771) and 92 for a single surgeon (range 11–293). The median rate of conversion to OC was 12 per cent (range 4–40 per cent). Overall 143 complications (2·2 per cent) were recorded: biliary injuries or stenosis 31 per cent, bile leaks 24 per cent, bleeding from gallbladder bed 14 per cent, haemorrhage from major vessels 7 per cent, deep abscesses 6 per cent, bowel injuries 5 per cent, retained CBD stones 5 per cent, wound infections 5 per cent, occlusions 2 per cent, anaesthesia or insufflation accidents 2 per cent. In 32 per cent of cases the complications were detected peroperatively and an immediate conversion to OC was performed. In 56 per cent of cases the complications were not detected during laparoscopy with a mean treatment delay of 3 ± 6 days (range 0–22 days). In these patients treatment was surgical in 80 per cent of cases (6 per cent laparoscopic) and percutaneous or endoscopic in 20 per cent. In this series, death occurred in six cases (0·009 per cent) (two bowel or vascular injuries, two bile leakages, two anaesthesia or insufflation accidents). Factors associated with an increased risk of complications were surgeon experience, cholecystitis or pancreatitis, obesity and lack of intraoperative cholangiography. An increased risk of post-complication death was significantly associated with the elderly (*P* < 0·001) and patient's thin body habitus (*P* < 0·001).
Conclusion: LC is a safe and valuable technique with a very low mortality rate (0·009 per cent) and a low complications rate (2·2 per cent)

Acute diverticulitis: laparoscopic treatment of complicated diverticulitis: report of 11 cases

L Potiron*, J.C. Berthout†, A. Morin*, E. Letessier‡ and J.C. Le Néel‡ **Clinique Mutualiste de Nantes, †Clinique Mutualiste de Lorient, and ‡University of Nantes, Clinique Chirurgicale A, Hôpital Hôtel Dieu, Nantes, France*

The surgical treatment of complicated diverticulitis remains controversial. Hartmann's procedure has been widely advocated in the presence of peritonitis. Alternatively, the operation of defunctioning colostomy and peritoneal drainage has been put forward by others. Interventional radiology is an effective technique in the management of selected cases of pelvic and intraabdominal abscesses. Laparoscopy today constitutes an approach to the diagnosis of acute abdomen.
Aim: The aim of this retrospective study was to address the question of emergency laparoscopy usefulness as first-stage procedure in case of complicated diverticulitis.
Methods: Eleven cases of laparoscopic treatment of complicated diverticulitis were performed. Laparoscopic findings were purulent peritonitis in one case, intra-abdominal abscess in seven cases, localized phlegmonous mass in three cases. The site of colonic perforation was identified in two cases and a sigmoid colostomy was elected in one case. All patients underwent drainage of the site.
Results: No mortality occurred. Surgical complications occurred in two cases. One case of intra-abdominal infection was cured by new drainage of the site through a new laparoscopy. One case of faecal leak through drainage tube occurred at day 3 and subsided on day 7 without further surgical treatment. Single-stage elective surgical resection was performed later in eight cases, including five cases of laparoscopic colectomy.
Conclusions: Laparoscopic treatment of acute diverticulitis including peritonitis can be effective and beneficial. The algorithm displayed in the paper provides a useful guideline for treating patients with complicated diverticulitis. In the light of the result obtained, the authors draw the following conclusions: (a) laparoscopic exploration should be reserved for those patients with obvious generalized peritonitis or after failure of conservative treatment, (b) the laparoscopic treatment should only be performed electively in purulent peritonitis or when diagnostic exploration shows an intra-abdominal abscess or a peridiverticular abscess

Laparoscopy in the diagnosis and treatment of complicated caecal diverticulitis

S. Rohr, N. de Manzini, O. Firtion and C. Meyer *Service de Chirurgie Générale et Digestive, CHU-Hautepierre, Avenue Molière, 67098 Strasbourg Cedex, France*

Caecal diverticulitis is a relatively rare disease in western countries. The preoperative diagnosis is difficult; the surgeon usually operates on for presumed acute appendicitis. The aim of this study was to present the laparoscopic approach in the diagnosis and the treatment of caecal diverticulitis.
Patients and methods: All cases of suspicious acute appendicitis were treated by laparoscopy from 1 January 1992 to 1 May 1996 (319 cases). Seven patients had complicated caecal diverticulitis (1·8 per cent).
Table 1 lists the cases:

No	Sex	Age (years)	Preoperative diagnosis	Laparoscopic diagnosis	Treatment*
1	M	54	doubtful appendicitis?	retrocaecal abscess	conversion caecum resection
2	F	35	appendicitis	caecal diverticulitis	conversion ileocaecal resection
3	M	45	right colon carcinoma	right colon carcinoma	by ileocolectomy under laparoscopy
4	F	28	appendicitis	caecal diverticulitis	conversion ileocaecal resection
5	M	34	appendicitis	caecal diverticulitis	conversion ileocaecal resection
6	M	39	appendicitis	caecal abscess	conversion ileocaecal resection
7	F	37	appendicitis	caecal diverticulitis	ileocaecal resection by laparoscopy

*Ileo-caecal anastomosis was made in all cases

Three ultrasonography examinations were preoperatively performed; all were considered normal. Case 3 had a barium enema and a colonoscopy which was suspicious of a right colon carcinoma. No patient was considered to have caecal diverticulitis preoperatively. We operated on for presumed acute appendicitis in five cases, for colon carcinoma in one case (No 3), the preoperative diagnosis was doubtful in one case.
Results: The laparoscopic approach allowed the correct diagnosis in four cases and resulted in a conversion in two cases. Carcinoma could not be ruled out in one patient (No 3). Laparoscopic ileo-colic resection was carried out in two cases. There were no deaths and no postoperative complications.
Conclusion: In this short series, the laparoscopic approach had, in the diagnosis of caecal diverticulitis, a sensitivity of 80 per cent and a specificity of 100 per cent. The laparoscopic treatment is feasible but the advantages are not proven.

Transperitoneal *vs* extraperitoneal approach in laparoscopic inguinal hernia repair: a prospective comparative clinical study

G.P. van der Schelling, L. Hendrickx, P. Goverde and R Van Hee *Academic Surgical Centre Stuivenberg, Antwerp, Belgium*

The aim of this study was to determine if the approach to the inguinal canal makes any difference in laparoscopic hernia repair regarding recurrence rate and morbidity. In a consecutive series of 70 patients we compared the transabdominal preperitoneal repair (TAPP) to the total extraperitoneal approach (TEPA). A total of 86 hernias were repaired in these 70 patients.

	TAPP	TEPA
No patients	32	38
No. hernias	35	51
Mean age	58 years	62 years
Complications	2	3
Conversion	1	4
Return to normal activity	21 days	11 days
Recurrence	1	1

Both laparoscopic techniques of inguinal hernia repair seem equally adequate in restoring inguinal canal anatomy. The recurrence rate and morbidity are not significantly different. Return to normal activity was significantly shorter in the extraperitoneal approach group. The higher conversion rate for the extraperitoneal route indicates a less steep learning curve for this technique. All conversions were in the first 10 procedures in both groups. In conclusion we think it is best to start with the transperitoneal approach to become acquainted with the anatomy. For more experienced laparoscopic surgeons the extraperitoneal route is preferable.

Comparison of laparoscopic cholecystectomy with long (>180 min) and short (<90 min) operative time

I.C. Spanos, I. Gatis, A. Ketentzoglou, K. Koutsopoulos, P. Chatzidimitriou, D. Papapavlou, T. Triantaphyllou, G. Pipis and P. Diacogeorgiou *2nd Surgical Department, General Hospital of Rhodes, Rhodes, Greece*

The goal of this work is the investigation of the consequences of the long operative time in laparoscopic cholecystectomy (LC), compared to LC with short operative time. Since 26 June 1992, 25 LC with operative time >180 min (Group A) and 190 LC with operative time <90 min (Group B) were performed in the 2nd Surgical Department, out of a total of 340 LC which have been done without any selection of the patients. The following parameters were evaluated. Sex, age, body weight, previous operations; co-existing diseases; intraoperative findings; postoperative course. The intraoperative findings were:

cholelithiasis	>180 min:	8 (32%),	<90 min:	122 (64%)
acute cholecystitis	,, :	11 (44%),	,, :	59 (31%)
hydrops of g.b	,, :	2 (8%),	,,	5 (2·6%)
empyema of g.b.	,,	2 (8%),	,, :	3 (1·6%)
small atrophic g b.	,, :	2 (8%),	,, :	1 (0·5%)

The operative time in Group A was 180–240 min with mean time of 200 min and in Group B was 30–90 min with mean time 55 min. Complications in Group A were one bile leakage of 1 week duration and in Group B none. Postoperative hospitalization time in Group A was 22–36 h, mean time 30 h and in Group B 18–24 h, mean time 20 h.
Conclusion: The long operative time in difficult LC does not adversely affect the postoperative course, if there are no severe co-existing diseases

Transabdominal preperitoneal approach in the management of inguinal hernia complications resulting from the procedure

A Stanek, Z. Wajda, Z. Sledziński, R. Marczewski, T. Wysocki and A. Basiński *II Department of Surgery, Medical University of Gdańsk 1, Prof. Kieturakis St., 80-742 Gdańsk, Poland*

In the early period of laparoscopic surgery most institutions only performed laparoscopic cholecystectomy The next step in the advance of laparoscopic technique was the introduction of laparoscopic herniorrhaphy (LH). A few modifications of LH were used. The most popular one is Transabdominal Preperitoneal Approach (TAPP) using prosthetic mesh to cover hernia defects. Between July 1992 and March 1996, 81 patients underwent LH using TAPP. There were 75 men and six women with a mean age of 41 ± 13 years. There were 71 indirect and 20 direct hernias In 10 cases there were bilateral hernias. All the patients were operated on laparoscopically using a transabdominal preperitoneal approach. Median operative time was 95 min (38–230 min) The patients were examined postoperatively during hospital-stay and on postoperative day 7, at 1 month and 1 year after the procedure. One intraoperative complication was noticed, injury to inferior epigastric artery which was managed laparoscopically. Perioperative complications following TAPP included: neuropathy in two patients, small bowel obstruction in one patient, haematomas in two patients, trocar site infections in three cases. Two patients developed recurrent inguinal hernias approximately 6–9 months after the procedure Both of them were reoperated on in the conventional way. Laparoscopic hernioplasty is a new and valuable modification of herniorrhaphy, but is not without complications

Changing modalities in laparoscopic cholecystectomy

A. Stavrou, P. Markidis, S. Stylogiannis, R. Nafas, C. Kontaxis, G. Micros, A. Tsapalos and J. Poulantzas *4th Surgical Department of 'Evangelismos' Hospital, D. Kintzonidis, 45–47 Ypsilantou Str., Athens, Greece*

The aim of this study is to present the changing modalities and outcome in laparoscopic cholecystectomy over the last 4 years since its introduction in our unit.

Between April 1992 and March 1996, 1486 cholecystectomies were performed in our department amongst which 367 were laparoscopic (24·7 per cent) The percentage of laparoscopic cholecystectomies has increased from 10·4 per cent in the first year to 61 per cent during the last year.

The spectrum of indications has been broadened from asymptomatic cholelithiasis in 1992, to include acute cholecystitis, empyema and common bile duct stones. Obesity, advanced age and cardiorespiratory problems are no longer reasons for exemption Contraindications nowadays include. peritonitis, cirrhosis, severe coagulopathy, cholecystoenteric fistulas and glaucoma

The conversion rate decreased from 10·7 per cent in the first year to 3·9 per cent in the last year Operating time decreased from a mean of 112 min to a mean of 75 min. Mortality was 0 per cent. Complication rate decreased from 11·2 per cent to 6·7 per cent. Major complications requiring laparotomy occurred in five cases. They were three cases of haemorrhage, a case of common bile duct injury and a case of persistent bile leak. Five patients underwent postoperative ERCP for residual choledocholithiasis. There were two cases of carcinoma of the gallbladder for one of which laparotomy and hepatic wedge resection was performed. Mean postoperative hospital stay decreased from 2·4 days to 1·5 days.

In conclusion laparoscopic cholecystectomy is now a well established procedure with few contraindications and low complication rates, and is the method of choice even in selected emergency cases.

Choledocholithiasis: two-stage treatment, ERCP with sphincterotomy and subsequent laparoscopic cholecystectomy

F Carbonell Tatay, C. Herrero Bernabeu, J. Del Pino Porres, J.L. Ponce, R. Estevan, R. Sancho, S. Fornos, V. Pertejo Pastor and T. Sala *Department of General and Digestive I, University Hospital La Fe, Valencia, Avda. Campanar 21, 46009 Valencia, Spain*

Aim: To evaluate the efficiency of the boarding combined on two occasions, firstly endoscopically and thereafter laparoscopically in the treatment of common bile duct lithiasis
Methods: Patients diagnosed by ultrasound or those who are suspected of harbouring a common bile duct stone are submitted to ERCP for exact diagnosis In case of confirmation sphincterotomy is performed There-

after laparoscopic cholecystectomy was performed 48 or 72h after the ERCP

Results: Sixteen patients, 10 male and six female Mean age was 59 years, and mean stay after laparoscopic cholecystectomy was 3 days Average duration of operation 90min (50–135min)

Conclusions: Our results, although with a small number of cases, suggest a combined approach is useful in the management of confirmed or suspected CBD stones.

Laparoscopic splenectomy using a lateral approach

A Valeri, L. Presenti, P. Tonelli, A. Todaro, F. Venneri and D. Borrelli *II° U O. Chirurgia Generale e Vascolare, Policlinico di Careggi-Firenze, Viale Morgagni, 80 Firenze, Italy*

Laparoscopic splenectomy was first introduced by Delaitre in Paris and by Carroll in Los Angeles in 1991 This procedure has been increasingly performed ever since thanks to the improvement of laparoscopic instruments We perform laparoscopic splenectomy in our surgical ward using this approach in young patients affected by idiopathic thrombocytopenia (ITP) and autoimmune haemolytic anaemia.

The patient is placed in a right lateral position and 4–5 cannulas measuring 10–12mm are used for access A 30° videocamera is inserted through the umbilicus according to the 'open' technique The surgical stages were the following: cutting splenocolic and left lateral peritoneal ligaments; ligation of splenic vessels using an endoGIA device; short gastric vessels are cut between clips and the spleen is fragmented within an endobag and then removed; a drainage tube is placed.

The technical suggestions we propose are the following: the lateral position of the patient upon the operating table facilitates retraction of spleen, we avoid tying the splenic artery beforehand and limit preventive dissection of middle splenic vessels This last step is achieved using vascular suture devices placed very close to spleen parenchyma assuring good haemostasis and avoiding the risk of accidental vascular lesions which occur very frequently when the surgeon is dissecting the blood vessels.

We performed laparoscopic splenectomy during the last 10 months in 6 patients, five of whom were affected by ITP and one patient presented autoimmune haemolytic anaemia, without requiring blood transfusions and the necessity to convert to laparotomy

Assessment of the indications for preoperative endoscopic retrograde cholangiography (ERC) in laparoscopic cholecystectomy

P. Willemsen*, I. Tielliu*, M. Vanderveken* and J. Holvoet†
*A.Z. Middelheim, Department of *General Surgery and †Gastroenterology, Lindendreef 1 B-2020 Antwerp, Belgium*

Aim: Assessment of the indications for pre-operative ERC in laparoscopic cholecystectomy.

Methods: Between January 1991 and October 1995, 501 patients underwent a successful laparoscopic cholecystectomy in our department. All patients with abnormal liver function tests and/or abnormal bile ducts on ultrasound had a preoperative ERC and endoscopic bile duct clearance if stones were present One hundred and thirty-four patients were identified who had a preoperative ERC Twenty-two of these patients proved to have common bile duct stones (CBD stones). The case notes of these patients were further analysed. Thirteen patients had a postoperative ERC The case notes of these patients were analysed as well

Results: Of the 22 patients with preoperatively diagnosed common bile duct stones 19 (86·2 per cent) presented with either biliary pancreatitis, cholangitis or persisting jaundice and abnormal liver function tests Two of the remaining three patients only had small CBD stones (<5mm) The final patient was an inpatient in a psychiatric hospital and history taking and proper examination was difficult In all 22 patients preoperative endoscopic bile duct clearance was successful Thirteen patients had an ERC post-laparoscopic cholecystectomy for persisting complaints Six of them had retained CBD stones (4) or signs of recent stone passage (2). Of these patients three had a negative preoperative ERC One patient had proven biliary pancreatitis was operated on as an emergency without preoperative preparation ERC. The four patients with retained CBD stones underwent endoscopic CBD clearance. Six patients did not have CBD stones or CBD-related pathology. One patient proved to have an iatrogenic CBD lesion. He was treated endoscopically

Conclusions: A preoperative ERC is mandatory in patients at risk for CBD stones These are patients with either biliary pancreatitis, cholangitis or persisting jaundice and abnormal liver function tests. In experienced hands endoscopic CBD clearance is an excellent way of treating CBD stones.

Iatrogenic complications after abdominal laparoscopic procedures

K. Ziaja, M. Kazibudzki, M. Zaniewski, J. Samorodny and M. Tochowicz *Department of Geneal and Vascular Surgery, Silesian Medical School, 40-635 Katowice ul. Ziołowa 45, Poland*

The paper presents three early and two late iatrogenic complications following laparoscopic procedures in abdominal cavity Early complications consisted of damage to large vessels, with concomitant injury of the gastrointestinal tract in one case. The vessels were reconstructed surgically In two patients the postoperative effect was good In one case, three further operations were necessary due to necrosis of the gastrointestinal tract and a retroperitoneal abscess. Two late complications were stricture of the common bile duct. The stenosed segments were surgically excised and anastomosed end-to-end. The authors also emphasize the necessity of employing extended diagnostic management prior to laparoscopic procedures in cases where another disease of the abdominal organs is suspected. Two patients were diagnosed with non-resectable pancreatic tumour 4 and 8 months after laparoscopic cholecystectomy and one with advanced cancer of the stomach 6 months after laparoscopic procedure

Laparoscopic cholecystectomy without any major bile duct injury with selective cholangiography: experience of 420 cases

A. Zorluoğlu, T. Yılmazlar, C. Aşcı, T. Kirdak and O.A. Dogan *Uludağ University School of Medicine, 16059 Bursa, Turkey*

We reviewed 420 patients who underwent laparoscopic cholecystectomy at the Department of General Surgery, Uludağ University Medical Faculty, between November 1992 and May 1996.

The male to female ratio was 130/290 Median age was 50 (19–82) years. Of the 420 patients who underwent laparoscopic cholecystectomy 351 (83·5 per cent) had chronic calculous cholecystitis, 27 (6·5 per cent) had acute calculous cholecystitis, 11 (2·6 per cent) had gallbladder polyp, 29 (6·9 per cent) had asymptomatic gallstones, one had cholelithiasis with concurrent choledocholithiasis and one had pancreatic tumour. In 32 (7·6 per cent) cases, it was necessary to convert open cholecystectomy due to intraoperative bleeding, difficult dissection, dense intra-abdominal adhesions, choledocholithiasis, unclear anatomy and syncronous colonic tumour. Twenty-four (5·7 per cent) patients who had high bilirubin and/or alkaline phosphatase levels or history of jaundice or unclear anatomy had intraoperative cholangiography, and 10 (2 4 per cent) patients underwent endoscopic retrograde cholangiopancreatography (ERCP) preoperatively. Two (0·4 per cent) patients underwent a second operation due to cystic duct leakage and perforation of duodenal diverticula Only one mortality occurred from septicaemia due to perforation of duodenal diverticula. Mean hospital stay was 28h (12h–6 days).

In conclusion, excluding the patients with high bilirubin and/or alkaline phosphatase (ALP) levels or history of jaundice, it is not necessary to perform routine intraoperative cholangiography during laparoscopic cholecystectomy to avoid major bile duct injury.

Liver

The effects of GCS-F on neutrophil phagocytosis index in experimental obstructive jaundice

H. Analay, Ş. Gokgoz, C. Yıldırır, B. Dalkılıç and M. Can
Cumhuriyet University General Hospital, Department of General Surgery, Sivas, Turkey

Septic complications are frequent in obstructive jaundice. Several studies have shown that the absence of bile salt drainage to the intestine, the spoil of intestine mucosal composition, the spill-over of gut derived to the systemic circulation as a result of the phagocytosis impairment of endotoxins and the bacteria that passed into portal circulation by the liver Kupffer cells, can be effective on these symptoms. Also, the depression of the mononuclear phagocytic system and the deficiency humoral and cell-mediated immunity are also effective on these septic complications.

In our study, we used 50 Sprague–Dawley rats (200–300g). Group 1, sham ligation ($n = 10$); Group 2, bile duct ligation (BDL, $n = 20$), Group 3, BDL + 30µg/kg/day GCS-F, i.m ($n = 20$). Under ether anaesthesia central upper incision was performed, the common bile duct was identified, doubly ligated with 4-0 silk ligatures and divided. After 21 days blood samples were taken by cardiac puncture. The neutrophil phagocytosis were examined by modified Brandt method, and the results are shown in Table 1

	Neutrophil phagocytosis index
Group 1	160 ± 10
Group 2	70 ± 10
Group 3	90 ± 10

While the difference between Group 1 and Group 2 was statistically significant ($P < 0.01$), there was no significant relationship between Group 2 and Group 3 ($P > 0.05$)

TIPSS in liver transplant candidates

F.A. Bartoli[*,†], L A. Aldrighetti[†], N. Jabbour[†], A.B. Zajko[‡], A. Leggio[*] and J.J. Fung[†] [*]*Paediatric Surgery, University of Bari, Italy;* [†]*Pittsburgh Transplantation Institute and* [‡]*Department of Radiology, University of Pittsburgh, Pittsburgh, PA, USA*

Aim: To analyse the effects of transjugular intrahepatic porto-systemic shunt (TIPSS) in liver transplant (OLTx) candidates.

Materials and methods: Sixty-eight cirrhotic patients underwent TIPSS between September 1991 and September 1993. Indications for TIPSS were acute or recurrent variceal bleeding in 67 patients and intractable ascites in one patient. All patients were classified using the Child–Pugh classification. TIPSS was performed in all cases with the standard technique. After TIPSS, all patients were evaluated for OLTx. Technical complications, post-TIPSS hepatic encephalopathy (HE), recurrent haemorrhage (RH), shunt stenosis (SS), renal function, infections and deaths were analysed. HE, RE, and SS were compared with porto-systemic gradient (final PSG more or less than 12mmHg, percentage of reduction in PSG more or less than 50 per cent), age (more or less than 50 years), Child class (A + B *vs* C)

Results: The TIPSS procedure, attempted in 70 patients, was successful in 68 (98 per cent); unsuccessful procedures were due to the failure in cannulating the portal vein system. The mean follow-up time was 299 ± 243 days after TIPS. Using the Child–Pugh score, 11 were Class A, 39 were Class B and 18 were Class C. Palmaz stent was used in 23 patients, while Wallstent was inserted in 45 cases. Following TIPSS, the mean PSG dropped from 25 ± 5mmHg to 10 ± 4mmHg, with a mean PSG percentage reduction of 60 per cent ± 12 per cent. HE developed or worsened in 23/68 patients (34 per cent). The incidence of HE was greater (38 per cent *vs* 19 per cent) in patients achieving a reduction in PSG $\geq$ 50 per cent of the pre-TIPSS value. RE occurred in 15 patients (22 per cent), and correlated with SS in 40 per cent of cases. The incidence of RE was lower (15 per cent *vs* 33 per cent) in patients with final PSG < 12mmHg, and slightly greater in Palmaz stent TIPSS (39 per cent *vs* 31 per cent), when compared with Wallstent cases. RE was successfully treated with medical therapy in 10 cases (66 per cent), while five cases (34 per cent) required angioplasty or new stenting procedure. RE and HE following TIPSS were not statistically associated with age or Child–Pugh classification. Post-TIPSS SS was observed in 23 patients (34 per cent). The majority (76 per cent) occurred during the first 6 months following TIPSS. Renal function deterioration occurred in nine patients (13 per cent). Other complications included: two stent misplacements and two persistent variceal haemorrhages. Out of 68, 56 patients were eventually deemed candidates for OLTx. Eight out of 68 patients (12 per cent) died prior to OLTx. Infections were primary contributing cause of death. Twenty-five out of 56 (45 per cent) patients listed for OLTx, eventually received OLTx. The mean elapsed time between TIPSS and OLTx was 144 ± 239 days.

Conclusions: TIPSS appears to be a safe and useful non-surgical procedure in the management of acute and recurrent variceal haemorrhage and ascites in patients awaiting OLTx, with minimal technical risks and failure.

Oesophageal transection for variceal bleeding in patients with extrahepatic portal thrombosis: late results

J. Baulieux, N. Berthoux, M. Adham, E. De La Roche, I. Mechet, C. Ducerf and M. Pouyet *Department of Gastrointestinal Surgery and Organ Transplantation, Hospital de la Croix Rousse, Lyon, France*

Extrahepatic portal thrombosis with normal liver function is a rare condition in adults. Variceal bleeding in such patients is the commonest mode of presentation, almost 90 per cent of them will bleed during evolution.

We report on our experience of oesophageal transection between January 1977 and January 1995. During this period, seven patients were treated for variceal bleeding with extrahepatic portal thrombosis. The diagnosis was made with coelio-mesenteric angiography in six cases and splenoportography in one. Surgery was performed after sclerotherapy and medical means failure. We chose a non-shunting technique because of massive portosplenomesenteric involvement. In a case we used the technique of oesophageal transection with a circular stapling after devascularization of the lower oesophagus and ligation of the left gastric vein. Rebleeding is frequent (five patients rebled) but all the patients are alive with a mean follow-up of 73 months (7–150 months). Sclerotherapy and medical means were successful on rebleeding. Oesophageal transection seems to be interesting in extensive extrahepatic portal thrombosis with results as good as those with makeshift shunts. Mortality and morbidity are acceptable. Surgery has to be a second-line treatment because of the good acceptance of bleeding episodes probably due to normal liver function. If shunting procedures are possible, they are probably the best surgical method on rebleeding rate but require a patent splenic or mesenteric vein

TIPS *vs* endoscopic sclerotherapy (ES) for prevention of variceal bleeding: final report of randomized controlled trial

A. Bolognese[*], M. Cardi[*], L. Capocaccia[*], S. Salvatori[*], O. Riggio[*], M. Merli[*], I A. Muttillo, R. De Franchis[†] and F. Fiaccadori[‡] [*]*Università 'La Sapienza' Roma;* [†]*Osp Maggiore Milano,* [‡]*Università di Parma, Parma, Italy*

Eighty-one of 122 consecutively observed cirrhotics were randomized, following cessation of bleeding, to TIPS (38) or ES (43). Portal vein thrombosis, diffuse HCC, cardiac failure, previous multiple ES session were causes of exclusion The risk of rebleeding-randomization interval was 1–7 days, 1–6 weeks, 7–24 weeks Randomization was by sealed envelope, with a recurring block size of four. TIPS or ES were scheduled within 1 week from randomization. ES was repeated at weekly intervals until variceal eradication. Clinical examination, Doppler US and endoscopy were repeated every 6 months In the TIPS groups, portography was performed at 6 months and every time shunt malfunction was suspected. Rebleeding from any source was the primary endpoint Sample size ($\alpha = 0{\cdot}05$, $\beta = 0{\cdot}90$, 75 per cent reduction of rebleeding) was *a priori* established to be 38 patients per group. Secondary endpoints were deaths from any cause, encephalopathy (HE) and other complications The two groups were comparable for age, sex and Child-Pugh. Mean follow up was 18 ± 9 months Eighty-seven per cent of patients in the TIPS and 91 per cent in the ES group received the assigned treatment (TIPS: one refused, two died before treatment, two technical failure, ES. one refused, two died before treatment, one not treated for complication). Data were analysed according to the intention to treat Cumulative rebleeding rate at 1 year was lower in TIPS (21 ± 7 per cent s e m.) than in ES group (52 ± 8 per cent; $P = 0{\cdot}011$). Overall, 12 rebleeding episodes (seven from varices) occurred in TIPS and in 10 patients (12 episodes) in ES group had HE during FU ($P = 0{\cdot}001$). Three episodes in ES groups and eight episodes in the TIPS group were grade 3–4. Shunt malfunction was observed in 22 patients, and 12 patients suffered more than one episode of their stenosis or occlusion It can be concluded that the use of TIPS is not justified in patients with one previous episode of bleeding from EV

Surgical treatment of giant haemangiomas

G. Borgonovo, F. Razzetta, A. Arezzo, M. Puglisi, G.C. Torre and F.P. Mattioli *Istituto di Clinica Chirurgica, Università di Genova, V. le Benedetto XV 8, 16132 Genova, Italy*

Haemangiomas are the most common benign liver disease. Cavernous haemangiomas more than 4 cm in diameter are defined as giant haemangiomas and can be of clinical interest The indication to surgery and correct surgical strategy of giant haemangiomas of the liver is debated. Surgery is based on two main techniques. resection and enucleation. From 1982 to 1990, seven patients with symptomatic giant haemangiomas underwent typical hepatic resection Pain in the right hypocondrium was the most frequent symptom Haemoperitoneum was present in an elderly patient. Hepatectomy was carried out after extraparenchymal ligation of the hilar structures In the last three patients the peritoneal cavity was not drained Three right hepatectomies, one right extended hepatectomy, one left hepatectomy and two left lobectomies (segments 2 and 3) were performed Estimated blood loss ranged from 350 to 1000 ml with a mean loss of 714 ml No major postoperative complication and no long-term sequela occurred Two episodes of cholangitis in the elderly patient after emergency operation were resolved with medical treatment Enucleation is a sure and radical method, but requires a complete mobilization of the liver in case of large lesions and previous reports have shown the number of required transfusions to be not negligible In our experience of typical resection blood loss was slight in most cases and transfusion of heterologous blood was rarely required Enucleation is an option when the lesion is small and superficial In the case of large and deep haemangiomas in proximity of vascular structures, typical liver resection is a safe operation entailing lower morbidity and blood loss than enucleation

The expanding options in the management of hepatocellular carcinoma (HCC)

J Briceño, P Lopez-Cillero, M Delgado, C Diaz-Iglesias, S. Rufian, E Espinosa, G Solorzano, M. De La Mata, G. Miño and C Pera *Departamento de Cirugía (6ª planta), Hospital Reina Sofía, Avenida Menéndez Pidal s/n, 14004 Córdoba, Spain*

Introduction: HCC remains difficult to treat and, in the past, has had a poor prognosis. In our historical series, 30 per cent of the patients with HCC accepted for surgical treatment were irresectable after laparotomy. The appearance of currently available treatment modalities suggests that some improvements may already be available.

Aim: The objective of this study was to review prospectively the efficacy of the different treatment options in the management of these tumours.

Methods: From January 1993 to May 1996, a total of 171 patients were affected with an HCC. Forty-three (25 per cent) were accepted for a modality of treatment with the following indications: (a) partial hepatic resection ($n = 10$): patients with an HCC less than 5 cm, a number of tumour nodules fewer than three, located in the same lobe, capsulated tumours, a good liver function (A5-Child), and absence of vascular invasion. (b) Orthotopic liver transplantation (OLT) ($n = 11$). HCC with a 3–5 cm diameter; liver dysfunction (B- or C-Child) and less than 60 years old. (c) Percutaneous ethanol injection (PEI) ($n = 10$). a diameter less than 4 cm, no more than three isolated nodules, when partial resection or OLT were contraindicated. (d) Transarterial chemo-embolization (TQE) ($n = 14$). tumours with a diameter more than 5 cm; good liver function tests (A- or B-Child), younger than 65 years, in patients with tumoural recurrence after resection or OLT or with a technical difficulty for PEI

Results: Mean follow-up was 10 months (1–36 months) with 11 deaths (25 per cent) and the survival shown in Table 1 determined by Kaplan–Meier method:

	6-month survival	1-year survival	Deaths	Recurrences
Resection	90 per cent	90 per cent	1/10	4/10
OLT	75 per cent	72 per cent	3/11	0/11
PEI	70 per cent	54 per cent	4/10	0/10
TQE	76 per cent	74 per cent	3/14	0/14

Conclusions: OLT has become an increasingly acceptable treatment in our series as has TQE. Partial resection is accompanied by a good survival with a high recurrence rate. PEI has a worse prognosis which may be related to other clinical parameters not exclusively dependent on HCC

Protective effects of aprotinin on ischaemia/reperfusion-induced liver injury in rats

N Z. Canturk*, N.Z. Utkan*, M. Dulger*, C. Yıldırır†, E. Düzcan‡ and N.N. Gönüllü* **Kocaeli University, †Cumhuriyet University, ‡Pamukkale University, School of Medicine, Turkey*

Aim: Protecting the liver against ischaemic injury is a major concern in hepatic surgery This study was designed to evaluate the effect of aprotinin on hepatic ischaemia/reperfusion injury.

Material and methods: Albino rats of Wistar strain were allocated to three groups as follows: sham group (SG); control group (CG); and aprotinin group (AG) In each group, every rat was exposed to 1 h of ischaemia and 45 min reperfusion. Every rat in AG was pretreated 40,000 KIU aprotinin. The biochemical and microscopic parameters were determined at the end of the experiment. All rats were observed for 7 days postoperatively for determination of survival

Results: The elevation of SGOT and SGPT values was reduced in the animals with aprotinin pretreatment in comparison with the control group. Histological alterations were not similar to biochemical value during the early phase.

Conclusion: Our results indicated that premedication with high doses of aprotinin provided highly protective effects against normothermic ischaemia and reperfusion injury model Aprotinin pretreatment of donors is able to prolong the ischaemic tolerance time of the grafts

Solitary necrotic nodule of the liver: diagnosis and management

C. Carriero, S. Alfieri, G.B. Doglietto and F. Crucitti
Department of Surgery, Catholic University, Rome, Italy

Solitary necrotic nodule of the liver is an uncommon lesion with an uncertain pathogenesis The possibility of a single necrotic metastasis is often but erroneously taken into consideration A 59-year-old woman was referred to us for asymptomatic nodular lesion of the liver, discovered incidentally at ultrasound examination during a check-up. Serum CEA, TPA, Ca 19·9, alpha-fetoprotein levels were normal as well as haematological examination Two percutaneous biopsies were unremarkable. Ultrasonography, CT scan and MRI revealed a 35-mm wide lesion located in segment VI of the liver. The lesion was isoechoic with hypo-echoic halo at US examination; hypodense with central calcification on CT scan with mild peripheric enhancement after bolus injection. Axial T2 weight MRI image showed a hypo-intense focal liver lesion with slightly hyperintense central area; T1-weighted gradient echo-image during the arterial phase of the dynamic scan showed a hypo-intense lesion with a peripheral hyperintense rim. The imaging examination's results pointed to a secondary liver tumour. Clinical and instrumental research for a primary lesion was unsuccessful. Inability to exclude malignancy has then been considered an indication for a laparotomy.

Results: Intraoperative ultrasonogram confirmed the hepatic lesion. The resection consisted of a segmentectomy VI. No other lesions (primary tumour) were found. Macroscopically the lesion appeared well circumscribed on the anterior surface of the liver, subcapsular, white on section. Histological features were a completely necrotic core with areas of reticulin and conserved vascular spaces surrounded by a dense collar of hyalinized collagen containing elastic fibres. The nuclei were usually round and regular. Mitotic figures were absent Parasitic infection was excluded with specific stains The diagnosis was a solitary necrotic nodule of the liver. The patient made an uneventful recovery. Three and 6 months later follow-up showed her to be free of any disease. Radiologists, pathologists and surgeons may have trouble with diagnosis and treatment of this solitary lesion of the liver: in fact for its radiological characteristics diagnosis is often as liver metastasis The pathologist must be aware of the possibility that this benign lesion might be misinterpreted as necrotic tumour on frozen or paraffin section. Solitary lesions in the liver should not be assumed to be metastasis if biopsy is negative even if radiological appearance is suggestive of a secondary tumour. The impossibility of making the differential diagnosis with instrumental imaging and the potential risk of a malignant secondary tumour makes liver resection recommended.

Surgical treatment of liver metastasis

E. Ciferri, G. Bondanza, S. Fazio, M. Filauro, C. Bagarolo, M. Castagnola, L. Mori and G.M. Gazzaniga *Ist Surgical Department, San Martino Hospital, Genoa, Italy*

Indication to surgical treatment for liver metastases is based on precise criteria that include their number, dimension, site, continuity/contiguity with important vascular structures and lymphnodal involvement. Preoperative staging is obtained by US/CT/MRI scan evaluation, CEA and Ca 19.9 dosage.

Between January 1980 and April 1996, we treated 189 patients (median age: 60 years; range: 35–82 years) for hepatic metastases: 145 from colorectal cancer, 44 from non-colorectal cancer (stomach, gallbladder, biliary tract, pancreas, carcinoid, adrenal gland, pelvic sarcoma, breast, oesophagus). We have operated on 159 patients Mortality and morbidity rates were, respectively, 3·7 per cent (six patients) and 19·4 per cent (31 patients). Five-year actuarial survival of colorectal and non-colorectal metastases were 24 per cent and 6 per cent, respectively.

In the cases without surgical indication we performed a schedule-oriented biochemical modulation of Fura bolus by MTX and Fura continuous infusion by Leucovorin, to reduce neoplastic lesions and infiltration. As of today we treated 17 patients obtaining three complete responses after 6 months of this chemotherapy. Two of these patients, in each of which two liver metastases had reached dimensions of 2cm in diameter, were operated, after a previous intraoperative US control, and are now free of disease 1 year after the operation.

Eleven other patients were reoperated on for colorectal repeated liver metastases with 18 per cent of 5-year global survival and a mortality rate of 9 per cent (one patient).

Higgins and Anderson hepatectomy in the rat using a microsurgical technique

M.C. Duran, G. Rodriguez, S. Alonso, H.J. Duran, L. Lorente, M.A. Aller and J. Arias *Department of Surgery, University Hospital 'San Carlos', Complutense University of Madrid, Spain*

Hepatic regeneration could be studied when different types of hepatectomies are performed in the rat. The two superior lobes hepatectomy in the rat, which comprise 65 per cent in the resection of the hepatic parenchyma, was described by Higgins and Anderson in 1931, using a macrosurgical technique.

A new experimental model of this hepatectomy in the Wistar rat (n = 16), but using a microsurgical technique (Olympus; 10 × 4 × 0·5) is described. At first, the hepatic hilum of the middle (ML) and left lateral (LLL) lobes, that is, the hepatic artery, the portal vein and the bile duct, were ligated together Next the falciform and posterior, right and left, ligaments of the liver were sectioned. The right hepatic vein, that drains the middle and the right portions of the ML, was sectioned between ligatures. The drainage of the middle hepatic vein, that drains into the SH-IVC the left portion of the right ML, is close to that of the left hepatic vein, that drains the left ML. This anatomic feature makes possible the ligation of both veins together without stenosis of the SH-IVC.

A body weight loss was experienced by the animals until postoperative day 5 and at 21 days after the operation the body weight was similar to that of the control rats. On postoperative day 21 the size and the weight of the liver were similar to those of the control animals, so regeneration of the non-resected hepatic lobes, right lateral (RLL) and caudate (CL) lobes, have restored the overall hepatic mass.

The 70 per cent hepatectomy using a microsurgical technique is the most suitable method to avoid the iatrogenic functional impairment of the remaining hepatic parenchyma.

Adenocarcinoma of the colon with liver metastases presenting with deep vein thrombosis: case report

M. Garatti, A. Bartoli and L. Vincenzi *Ospedale S. Orsola F.B.F, Div. di Chirurgia, Via Vittorio Emanuele II, 27 Brescia, Italy*

Recurrent Deep Vein Thrombosis (DVT) can be associated with an occult malignancy. The usual treatment for such condition is long-term anticoagulation which in many instances can contra-indicate radical surgical treatment especially when liver resection is needed

A 70-year-old man presenting with recent DVT was admitted to our department. a duplex scan of limbs showed complete occlusion of left femoral and popliteal veins. He was placed under i.v. heparin for 4 days and then systemic heparinization was discontinued after accomplishment of satisfactory oral anticoagulation (PT: 37 per cent INR: 2·28). During this period the patient developed left lower quadrant abdominal pain; a colonoscopy showed an infiltrating neoplastic lesion in the sigmoid colon. Abdominal ultrasound and CT scan showed a 4-cm lesion in the left lateral segment of the liver and a second one of 1·5 cm was in segment VII. In order to proceed with surgery, the patient was anticoagulated, a titanium Greenfield permanent filter was placed in the inferior vena cava, below the origin of the renal veins, and the anticoagulation was stopped At the laparotomy we found a left colon lesion involving a segment of small bowel; intraoperative ultrasonography confirmed the presence of liver metastases in the left lateral segment and in segment VII and two other additional lesions (1 cm and 1·8 cm) were also found in segment VIII. As soon as we demonstrated that the primary lesion was removable we performed an anatomic left lateral segmentectomy under portal clamping (10 min); wedge resections without portal clamping were performed for the lesions in segments VII and VIII. A left colon resection was then accomplished· 25 cm of the involved small bowel were resected as well.

The postoperative period was uneventful and the patient was discharged on postoperative day 12. At 1-year follow-up the patient is well and disease-free. This patient's history demonstrates that synchronous liver lesions from colon cancer can be safely resected even in patients with recent DVT in whom anticoagulation is incompatible with major surgery, provided that an alternative method for pulmonary embolism prevention is undertaken

Relation of portal haemodynamic disorders to the tendency to oesophageal bleeding

P. Małkowski, B. Michałowicz, J. Pawlak, R. Paluszkiewicz, I. Grzelak, T. Wróblewski and E. Leowska *Departments of Liver Surgery and Nuclear Medicine, The Medical University of Warsaw, ul. Banacha 1a, 02 097 Warszawa, Poland*

Aim: The authors try to investigate the relations between the portal system haemodynamic disorders detected by SG-Doppler, the size of gastro-oesophageal varices and their tendency to bleed

Material and methods: A group of 34 patients with portal hypertension due to pre-hepatic portal occlusion, but without history of bleeding, underwent a prospective analysis. The echo-Doppler investigation of portal system and collateral circulation was repeated every 2 months The size and extent of oesophageal varices were monitored at the repeated endoscopies The average time of observation was 12 months.

Results: In nine patients a significant enlargement of varices occurred It was accompanied by the development of hepatofugal collateral circulation, involving the region of cardia. Three patients, with the most advance changes, bled and underwent emergency sclerotherapy. One of these patients died, in one sclerotherapy was effective and one required a 'non-shunt' surgery. The remaining six patients, considered as potential bleeders, were treated by sclerotherapy without bleeding or any complications.

Conclusions: Progressing augmentation of oesophageal varices and development of hepatofugal collateral circulation announce the threatening haemorrhage. In these cases we consider prophylactic sclerotherapy as fully justified

Biliary complications in hydatid disease of the liver diagnosis and management by ERCP

R. Masetti, R. Coppola, A. Antinori, M.E Ricciomi, A. La Greca, S. Ciletti, P. Magistrelli and A. Picciocchi *Department of Surgery, Catholic University, Rome, Italy*

One hundred and forty-nine patients with hydatid disease of the liver were treated by surgery in our Department in the years 1982–1994 In 49 of these patients (33 per cent) a complication involving the biliary tract was suspected clinically prior to surgery They underwent preoperative ERCP (Group A) Eleven patients developed symptoms of biliary obstruction after surgery for the parasitic disease and underwent postoperative ERCP They constitute Group B of this review ERCP was successfully performed in all cases Starting from 1984, endoscopic sphincterotomy (ES) was associated in selected cases.

Group A (preoperative ERCP): There were 22 men and 27 women, ranging in age from 19 to 77 years (mean age = 50 years). Indications for ERCP included upper abdominal colicky pain in 23 patients, colicky pain and jaundice in 10, acute cholangitis in 14, and acute pancreatitis in two ERCP findings excluded biliary tract involvement in 16 cases. In the remaining 33 patients three different patterns of biliary involvement were shown· compression of the bile duct in 11 cases, small cysto-biliary communication in 10 cases and intrabiliary rupture in 12 cases At surgery, transcystic cholangiography was performed after treatment of cyst contents. Undetected communications between the cyst and the bile duct were seen in six of the 16 patients with negative ERCP findings (37·5 per cent) In seven of the 12 patients with intrabiliary rupture ES was performed followed by endoscopic removal of migrated hydatid material from the CBD.

Group B (postoperative ERCP): There were six men and five women, ranging in age from 34 to 74 years (mean age = 54 years). Indications for ERCP included acute cholangitis in three cases and persistent biliary fistula in eight cases. ERCP findings included residual hydatid material in the CBD in two cases, sclerosing cholangitis in three cases. ES was associated in nine cases both for removal of migrate hydatid material and for decompression of the biliary tree.

Conclusions: ERCP is useful both in the pre- and postoperative evaluation of patients with symptomatic hydatid disease of the liver. It allows for planning of proper treatment and in selected cases, if completed with ES, may eliminate the need for operative aggression of the CBD or renewed surgery.

Multifactorial pathomechanisms of portal hypertension

B. Michałowicz, J. Pawlak, P. Małkowski, O. Rowiński, R. Pacho, M. Andrzejewska and E. Leowska *Departments of Liver Surgery, Radiology and Nuclear Medicine, The Medical University of Warsaw, ul. Banacha 1a, 02 097 Warszawa, Poland*

Aim: To present the problems faced by a clinician treating the patients with oesophageal varices in case, when more than one cause of portal hypertension is found.

Material and methods: During the past 10 years among 620 patients treated for portal hypertension, 52 cases of liver cirrhosis coexisted with portal venous thrombosis ('double block') In five cirrhotic patients we found arterio-venous fistulas, causing an additional element of hyperkinetic hypertension In three cases the arterio-venous fistulas were situated in a neoplastic tissue of hepatoma, in one case in the cirrhotic liver tissue, in one case in the spleen. Intrahepatic arterio-venous fistulas were embolized, in a patient with arterio-venous fistula, splenectomy was performed

Results: In the 'double block' patients sclerotherapy was effective in 46 cases. Failure of sclerotherapy in eight patients was an indication for surgery. Three patients died after operation, five recovered. Embolization of arterio-venous fistulas in a hepatoma was successful in two cases, allowing the continuance of perarterial chemotherapy, in one case it was ineffective. The arterio-venous fistula in cirrhotic liver tissue were embolized successfully, but new fistula formation was noticed and the patient died Splenectomy in a patient with recent cirrhotic changes resulted in reduction of varices and absence of bleedings.

Conclusions: Coexistence of different pathological mechanisms causing portal hypertension creates serious problems while choosing the method of treatment in the cases of portal hypertension. In a 'double block' sclerotherapy is often unsuccessful and the patients require a 'non-shunt' surgical procedure Arterio-venous fistulas can be treated by embolization, although the result might not be long-lasting.

Comparison between two major hepatic resection procedures with or without liver vascular pedicle clamping

A. Parmeggiani*, S. Cimbanassi*, R. Rossi†, E. Ottoveggio*, L.R. Fassati* and D. Galmarini† **Cattedra Fisiopatologia Chirurgica †Ist Chir Gen, ‡E Catt Chir Sperimentale, Univ Stat, Milano, Osp Mag Pol, IRCCS, via F. Sforza, 35 Milan, Italy*

Aim: Pathophysiological analysis of the real motifs which may bring us to the choice of the best procedure in order to reach the best functional results in hepatic remnant.

Patients and methods: Twenty-five patients (12 males, 13 females, mean age 40·7 years) underwent liver resection; 11 for primary liver, one metastatic neoplasms, three benign liver tumours, 10 miscellaneous hepatic diseases. In our series we realized seven atypic resections, two lobectomies, 11 segmentectomies and seven hemihepatectomies Six patients underwent intermittent total vascular exclusion of the liver (ITVEL), with a duration of 15–40min Postoperative courses were uneventful except in three patients (biliary fistula and pleural effusion, haemoperitoneum, subdiaphragmatic abscess) Mean operative blood loss was 2350ml in four patients. Nineteen underwent intermittent partial vascular exclusion of the liver (IPVEL), with a duration of 5–60min Postoperative courses were uneventful except one case of biliary fistula Mean operative blood loss was 850ml per eight patients. Biochemical liver tests pre- and postoperatively tell about transaminases elevation from 47·1IU to 192·6IU within 7 days postoperatively Coagulation tests, counting even intraoperative haemodilution, ranged from 72·6 to 58·2 (7 days postoperatively) Changes in other parameters were insignificant

Both ITVEL and IPVEL patients showed bilirubin levels to increase by 0·9–2·1 only for 4 days. Both IVEL–IPVEL showed LDH elevation as well Haemoglobin pre- and post-liver resection, on postoperative day 2 decreased by 14–11.

Results: Notwithstanding ITVEL is always required to all major hepatic resections, we may conclude that biochemical *vs* enzymatic results showed clearly that IPVEL must be the choice of elective hepatic minor resections in order to prevent liver failure.

Conclusion: We may reasonably confirm that in our experience IPVEL prevents: haemorrhage from small alterations in coagulation factors; hypoglycaemia due to metabolic disorders; acidosis due to major liver perfusion maintenance; sepsis due to minor intestinal blood sequestration due to portal hypertension caused by vessel loop clamping.

Splenorenal shunt on liver cirrhosis with portal hypertension: for and against

M. Pavlovsky, S. Chooklin and A. Perejaslov *Medical Institute, Pekarska 69, 290010 Lviv, Ukraine*

Portal hypertension, which develops from liver cirrhosis, is frequently threatening by the bleeding from oesophageal varices, which in most cases have a lethal outcome. Splenorenal shunt remains one of the methods of prophylactic treatment of these bleedings However, as a rule, this does not take into account the immunological, hormonal and haemostasiological consequences of operation. A long-standing experience of liver cirrhosis patients who have undergone splenorenal shunting enables us to prove that this operation is not adequate on the given pathology. The haemodynamic factors are not enough. Appraisal of immunohormonal disturbances and changes in vascular–thrombocytic link of haemostasis show that in a given category of patients, liver damage had progressed, antigen stimulation and loading on liver was increased. Autoimmune processes were made active, the monocyte suppressor control was decreased, and the requirements in antidiuretic hormone were increased. Changes in eicosanoide synthesis supports the ischaemic changes in the liver. Changes in haemostasis system were typical for chronic DIC syndrome.

The lethal outcome was determined by pathological process progression, liver failure and haemocoagulative disturbances. The modification of Sugiura operation is the optimal alternative to splenorenal shunting

The cavoportal shunt in a gunshot wound

E. Piedrafita, J. Errando, P. Rebasa, G. Marín and L. Allende *Department of General and Digestive Surgery, Hospital de Sant Pau, C/. Sant Antoni Mª. Claret, 167, 08025 Barcelona, Spain*

Introduction: Trauma is the leading cause of death in people less than 35 years old[1]. Injuries at the retrohepatic vena cava can be difficult to manage so they show a mortality rate between 50 to 100 per cent. Although these injuries account for only 10 per cent of all liver injuries, they contribute notably to mortality in hepatic trauma[2] Due to their location, these injuries can be difficult to explore and to control.

Case report: A 31-year-old male patient was admitted our Emergency Department because of a gunshot wound. The patient was bradycardic, hypotensive and had 28 breaths/minute, the hole of the gunshot was located in the thorax and there was no exit hole. The patient immediately underwent an operation. There was a break in the left hepatic lobe, in the upper right kidney and a nearly complete section of the inferior retrohepatic vena cava. A left hepatic resection was performed (segments II and III), and an upper partial right nephrectomy with suprarenalectomy. The vena cava was repaired by means of a Dacron prosthesis. In order to complete vascular isolation, a clamp was placed across the infrarenal vena cava, the suprahepatic vena cava and both renal veins as well as the porta hepatis. Four days after surgery the patient had a thrombosis of the prosthesis of vena cava. He was reoperated on and the prosthesis was removed, the vena cava was cleaned and ligated. Circulation was restored by means of a cavoportal shunt end-to-end with Gore™ n 20. An acute renal failure appeared with normal isotopic renogram and normal pielography, it disappeared in a few days and no signs of thrombosis were seen. An echo-Doppler, 4 weeks after surgery, showed good flow through the shunt The patient was discharged 42 days after trauma, going on an anticoagulant therapy and in good health.

Discussion: Injuries of major vessels occur in 5 per cent to 25 per cent of patients with abdominal trauma and is the most common cause of death in these patients[3]. The most frequent is injury of the vena cava and it is associated with liver injuries and small bowel damage. The retrohepatic location has the worst outcome with a mortality rate nearly 86 per cent, followed by the suprarenal location (38 per cent), and the infrarenal location (10 per cent)[4]. Several techniques have been described to manage these injuries quickly and to repair the vena cava. The cavoportal shunt[5] may be a good technique with a low incidence of thrombosis and a good outcome for the patient.

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Predictors of hepatic failure after major liver resection: a prospective study of 100 cases

B. Pol, P. Campan, J. Hardwigsen, J. Pons and Y.P. Le Treut *Hopital La Conception, 147 Bd Baille, 13005 Marseille, France*

Aim: A prospective study is to determine the prevalence and cause of hepatic failure (HF) after major hepatic resection.

Patients: Between January 1988 and March 1995, 188 patients had hepatic resection. In 100 cases, three or more segments were removed, for primary malignant (36 cases), metastatic (35) or benign (29) tumours. Liver parenchyma was abnormal in 27 cases: cholestasis, major steatosis cases, fibrosis or cirrhosis, or hepatic vein obstruction. Hepatic resections included 44 right hepatectomies (RH), 23 extended RH, 20 LH, and 13 extended LH. Thirty-eight patients had an extra hepatic (i.e. colectomy) or peri-hepatic resection (i.e. bile duct resection) during the same procedure. Vascular inflow occlusion was used in 84 cases (mean duration 40 ± 15 min), and caval vein occlusion in 27 cases (mean duration 20 ± 13 min). Mean operative time was 242 ± 84 min. Seventy-three patients required blood transfusion (624 ± 698 ml). Mean weight of the specimen was 1022 ± 701 g.

Methods: Postoperative HF was considered present when serum bilirubin was higher than $100\,\mu m/l$ (except for cholestatic patients) and/or prothrombin time <50 per cent, during 3 or more consecutive days. Variables were analysed using χ^2 test and Mann–Whitney U-test.

Results: One or more postoperative complications occurred in 45 patients (with seven deaths), including HF in 12 cases (with four deaths). Three parameters were significantly correlated with HF: abnormal parenchyma. 29·6 per cent of HF *vs* 5·9 per cent on normal parenchyma ($P < 0{\cdot}001$), extended RH: 30·4 per cent of HF *vs* 3·2 per cent for other resections ($P < 0{\cdot}005$), and additional surgical procedures: 26·3 per cent of HF *vs* 3·2 per cent for plain hepatic resections ($P < 0{\cdot}001$). None of the other variables (age, tumour pathological type, number of resected segments, weight of the specimen, duration of vascular inflow occlusion, operative time, and blood transfusion) was significantly correlated with HF.

Conclusion: This study confirms that occurrence of HF is more frequent after extended RH, on abnormal liver parenchyma, and in cases of additional procedures. However, predictive factors of non-lethal postoperative HF remain to be defined.

Clinical presentation and diagnostic features of patients with hepatocellular carcinoma

M.G. Romijn*, D.J. Bac†, J.S. Laméris‡, H.W. Tilanus*,
S.W. Schalm†, W.C J. Hop§ and J.N.M. IJermans
Departments of General Surgery, Internal Medicine†,
Radiology‡ and Statistics§, Erasmus University Hospital,
Rotterdam, The Netherlands*

The survival of patients with hepatocellular carcinoma (HCC) depends on tumour size and liver status Patients with clinically apparent HCC have an advanced tumour and are generally not eligible for curative resection. Therefore, the diagnosis HCC should be made at an early stage when surgical resection may be curative. This study was initiated to evaluate the clinical presentation, diagnostic features, treatment and follow-up of patients presenting with HCC at the Hepatology Unit of our hospital

In a retrospective study data concerning medical history, laboratory and radiology findings as well as treatment and follow-up were collected From 1988 to 1995, 130 patients with a discrete nodule in the liver, presumed to be HCC, were admitted for analysis Thirty patients appeared to have a tumour of different origin or had no diagnostic work-up The population of patients consisted of 75 men and 25 women with an average age of 59 years (s d 13 years). Fourteen patients presented without symptoms Of the 86 symptomatic patients, 15 presented with pain, eight with tiredness and the other 63 with combinations of symptoms. Fifty-seven patients came from The Netherlands, 43 from abroad, mainly from countries where HBV is endemic. There was no correlation between AFP and survival. HCV-serology was positive in 11 patients, HBV-serology positive in 43 patients Twenty patients had a history of alcohol abuse without positive virus serology, and 87 patients were cirrhotic US as well as CT showed a mean tumour diameter of 5·6cm ± 3·2. Fifty-seven patients had a tumour <5cm, 11 of them <2cm. Fifteen patients appeared to have extra-hepatic metastases. After diagnostic work-up 24 patients were selected for surgery: nine segmental resections, eight hemihepatectomies and seven transplantations In the symptomatic group only a minority was eligible for curative resection The 1-, 3- and 5-year survival was 60 per cent, 34 per cent and 23 per cent in the operated group. In the non-operated group this was 26 per cent, 10 per cent and 0 per cent In the operated group there was a significant difference in survival between patients with a tumour <2cm and >2cm.

These results demonstrate that the majority of patients with HCC has an advanced tumour stage at the moment of presentation and only a minority is eligible for curative surgery by resection or by transplantation. Small tumours (<2cm) have a relatively good prognosis Screening of patients by US or AFP may increase the number of patients eligible for curative surgery

Hepatocellular carcinoma in cirrhotic liver: a comparison of MRI and CT scan in transplant patients

N.T. Schwarz, M. Wolff, J.C. Kalff, H. Schild and A. Hirner
Department of Surgery, University of Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany

Introduction: Long-term results of liver transplantation in patients with hepatocellular carcinoma (HCC) correlate with the tumour stage. The impact of tumoural lesions in cirrhotic livers detected postoperatively is unknown until now.

Methods: The occurrence of HCC in patients transplanted for liver cirrhosis was analysed retrospectively. Thirty-five patients with Child B and C cirrhosis and a median age of 48 years were examined. MRI was performed in 30 and CT scan in 35 patients. Both imaging modalities were assessed retrospectively by two independent radiologists, to determine the sensitivity and specificity of each technique. The median time between MRI or CT scan and transplantation was 78 or 50 days. The tumour localization in the explanted organ was compared with the preoperative diagnosis.

Results: Histopathologists found in 13 explanted livers 21 HCC of more than 0·6cm in diameter. The MRI detected 15 of 21 tumoural nodules in 10 of 12 patients In contrast, the CT scan revealed 11 of 21 tumoural lesions in 10 of 13 candidates There was no false-positive estimation The results of MRI and CT scan taken together, the comparison with portal-CT and sonography did not reveal any further tumoural lesions.

Conclusion: There was no significant difference between MRI and CT scan in the detection of HCC in cirrhotic livers, probably due to the small number of patients. MRI seemed to be more sensitive Portal enhanced CT is not suitable for the detection of HCC in liver cirrhosis. Probably, CT scan should be replaced by MRI and not be used additionally to decrease costs. We will continue to use the MRI in a prospective study in the evaluation of liver transplantation

Experimental measure of the tensile strength of biological sealant-collagen association after hepatectomy in dogs

M. Scotté, F. Dujardin, A. Annelot, P. Azema, I. Leblanc,
P. Bouvier, F. Michot and P. Ténière *GBPDN, ESIGELEC, CHU Rouen 76031, France*

Different treatments of liver cross-section after hepatectomy have been described, e.g. epiplooplasty, use of collagen patch and/or biological sealants The principle of the fibrin sealant is to obtain a fibrin clot. The adhesive property of this fibrin clot is an essential characteristic of the haemostatic sealant. The aim of this study was to measure the tensile strength of biological sealant-collagen association after hepatectomy in dogs in realistic surgical conditions

The experimental model have been previously described [1] After hepatectomy in dogs, the principle of the method was to measure the rupture stress point of a small wooden cylinder bonded on the liver cross-section with a Tissucol® (Immuno) solution. After bonding on the cross-section, the cylinder was pulled at a constant speed of 3mm/mn. A sensor was placed on the experimental set up and measured the applied strength Measure was performed until disruption of the experimental set-up.

Sixteen measures were performed in four dogs. The mean force measured was 0·27 ± 0 08 Newton No significant difference was observed between the different measures performed in each dog and between the four dogs. The maximum tensile strength measured with our model was 10 times higher than the force of the blood flow in a 2-mm diameter vessel in which blood pressure is 100mmHg These results indicate that fibrin sealants are effective in preventing postoperative blood loss after hepatectomy Our experimental model makes it possible to compare the different fibrin sealants or other sealants used in clinical practice.

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Hepatic cholangiogastric anastomoses in Klatskin tumours

F. Ticmeanu *Interdepartmental Hospital, Department of General Surgery, Calea Mosilor 239, Bloc 45 A, Ap. 21, Sector 2, Bucharest, Romania*

Owing to the progress lately achieved in imaging diagnosis, a better selection is now possible among the patients with Klatskin tumours as to who should undergo surgical treatment.

Palliative surgical procedures, which are still widely used, are recommended in those cases with non-removable extensive tumours with metastases, or for patients in a poor condition, with multiple organic disorders due to their age and to the evolution of the disease

Of 85 patients treated for Klatskin tumours hepatic cholangiogastric anastomoses were performed in 35 cases Cases were selected following the above mentioned criteria In order to have the diagnosis confirmed, in all cases extemporaneous morphological examinations of the tumours, hepatic metastases and lymph nodes were performed. Intrahepatic cholangiographic investigations performed during the operation have evinced the convergence of the free hepatic ducts in all cases The following results were recorded: two deaths in the first 30 days, seven cholangic fistulas located on the anastomoses, running towards the exterior, which were treated conservatively, eight upper digestive haemorrhages generated at the level of the hepatic section, compensated through blood transfusions, which did not endanger the patients' lives at any moment The average survival expectancy was 8 months, and varied from 2 to 24 months.

We can conclude that this surgical approach is easy to perform and does not last too long. When the total length of the third hepatic segment is used for the anastomosis, the flow through the main duct as well as through the secondary ones is free, the stomach does not fall into the section, and due to its plastic qualities diminishes the risk of fistulas. It provides a reasonably comfortable life for the patients for the rest of their lives, because both the jaundice and the itching disappear.

It is therefore considered that in cases of jaundice caused by Klatskin tumours, where the patient is diagnosed and admitted to hospital too late, with a rapid fatal evolution, then the outcome of hepatic cholangiogastric anastomosis speaks in favour of its utilization in selected cases.

Hepatocellular carcinoma in a non-cirrhotic patient with haemochromatosis

J. De Tomás, A. Louredo, F. Turégano and A. Alonso
Servicio de Cirugía General I, Hospital General Universitario 'Gregorio Marañón', C/Doctor Esquerdo 46, 28007 Madrid, Spain

The development of a hepatocellular carcinoma in a non-cirrhotic patient with haemochromatosis has been scarcely documented Iron and other metals, such as copper, induce DNA changes in the hepatocytes that could promote malignant transformation in livers without cirrhosis

A 61-year-old man was referred to our hospital for treatment of a malignant hepatoma. He had worked in a coal mine for 36 years, drinking water from a local spring and his alcohol intake was about half a litre of wine per day .He was also a smoker and was diagnosed with third-degree silicosis On examination, he had a pigmented skin without signs of liver disease The liver tests values were normal, serum iron and ferritin values were 147 µg/dl and 446 µg/l, respectively He had no family history of liver disease and his genetic study was normal On MRI, a 4-cm mass was observed at the right hepatic lobe and the liver showed iron overload. The angiogram confirmed a hypervascularized lesion at that location, and the CT scan did not show disseminated disease A right hepatectomy was carried out without postoperative complications and the pathology report confirmed a well differentiated trabecular hepatocarcinoma with a third-degree haemosiderosis and without cirrhosis

It is well known that the work in the coal mines allows the abnormal exposition of iron compounds to underground waters The wines of his area have high concentrations of copper and iron, so both facts could explain the iron overload of our patient Liver biopsies without signs of cirrhosis do not exclude the risk of the development a malignant hepatoma in a patient with haemochromatosis It is advisable to carry out periodically a liver US and alphafetoprotein serum levels.

Immune response in liver hydatidosis: influence of characteristics of cyst

J. Torcal, M. Navarro, J.C Salinas, L. Larrad, C. Pastor, J. Ferrer, J. Román and R. Lozano *Servicio de Cirugía A, Hospital Clínico Universitario 'Lozano Blesa', Avda. San Juan Bosco, 15, 50009 Zaragoza, Spain*

The study of immune response in patients with liver hydatidosis is very important because it may be useful for diagnosis and continuation of evolution after non-radical surgery. None the less, the sensibility of tests show the 'non-response' or 'low-response' in some cases. Therefore, the aim of the present paper is to ascertain if the immune response is influenced by the number, size, daughter vesicles and location of cyst within the liver itself.

Patients and methods: Twenty-one patients with liver hydatidosis were studied before surgery (where we confirmed the diagnosis) (group LH: eight males and 13 females, mean age = 46·5 ± 19 years, range = 14–77 years). None of these patients received chemotherapy, surgery or biological response modifiers before the study. None of these patients was malnourished The percentages of CD3+, CD20+, CD4+, CD8+ and CD16+ cells (flow-cytometry using MoAb); the levels of immunoglobulins IgA, IgG, IgM, total-IgE, and complement factors C3, C4 and BF (nephelometry); specific-IgE against *E. granulosus* (IgEs) and the levels of cytokine IL-1, IL-2, IL-4 and TNF (ELISA using MoAb), were studied in peripheral blood on the preoperative day. The same variables were studied in 21 healthy volunteers (control group). The parametric Student's *t*-test; the Mann–Whitney *U*-test and Wilcoxon's signed rank test for non-parametric date were used to examine differences. Spearman's correlation test and Pearson linear correlation test were used to test comparisons and correlations. The significance level was taken to be $P <$ 0·05

Results: Patients with hydatidosis showed a significant increase of IgG, IgE, IgEs, IgG, BF, C3, IL-1 and IL-2 levels but a decrease of IL-1 ($P >$ 0·05) and TNF levels ($P <$ 0·001). IgG levels were correlated with IgE levels, and IgE and IgEs also showed a linear correlation, IL-4 levels correlated with IgG levels. We can observe an increase of TNF levels ($P <$ 0·05) and a decrease of BF, C3 and C4 ($P <$ 0·05) in patients with cysts with a wide opening in the biliary tract. When cysts showed daughter vesicles patients showed a significant increase of IL-1, IL-2, IL-4, IgG, IgE and IgEs levels, these variables showed a significant increase too, in patients showing cysts in the central area of the liver. Only a decrease of C3 levels was observed when cysts are multiple. When the cysts are larger an increase of IgE levels ($P <$ 0·05) and a decrease of BF and C3 levels (P $<$ 0·05) can be observed No significant relations were observed between immunological variables we have studied and characteristics of patients.

Conclusion: The immune response in patients with liver hydatidosis is closely influenced by the characteristics of cyst, and above all by the presence of daughter vesicles and the location cyst within the liver itself.

Surgical treatment of hepatic hydatid disease

N.Z. Utkan*, N.Z. Cantürk*, N.N. Gönüllü*, C. Yıldırır† and M. Dülger* *Department of General Surgery, Faculty of Medicine, *Kocaeli University, Kocaeli and †Cumhuriyet University, Sivas, Turkey*

Fifty-three patients with hepatic hydatid disease were treated at our hospital during a 5-year period. Of the patients, 39 were females and 14 were males Thirty-five patients (66 per cent) had a single cyst, and cyst(s) involved the right lobe of the liver in 38 patients. Abdominal discomfort or pain was the most frequent symptom (79 per cent) Physical examination of the abdomen revealed palpable abdominal mass or hepatomegaly in 30 (56·4 per cent) patients, while 22 (41 per cent) patients had no physical finding. Indirect haemagglutination test was positive in 28 (84 per cent) patients preoperatively, and in the postoperative period, it was found to be negative in 22 (66 per cent) patients. Diagnosis was confirmed by both ultrasonography and computed tomography in virtually 100 per cent of the cases.

All patients were treated surgically Partial cystectomy capitonage were performed in 29 patients with uncomplicated diagnosis. In 14 patients, communications between the cavity and the biliary tree were closed with absorbable sutures and T-tube drainage if the connection was large. Omentoplasty, alone in 12 (12·6 per cent) patients and together with partial cystectomy in 20 (21 per cent) patients, was performed after the removal of uninfected cysts. There were 23 (43·4 per cent) cases with postoperative complications. The most common complication was prolonged biliary drainage (15 per cent) in the early period, and cholangitis and jaundice in the later period (9·4 per cent) The most common complication was seen in the external tube drainage group.

The average hospitalization period was 11·5 (9·2–13·8) days. While this period was prolonged in the patients who underwent external tube drainage to 32·8 (17·1–48·6) days, the duration of the hospitalization for the omentoplasty and cystectomy groups were shorter at 9 (6·3–11·7) days.

Surgical treatment of hepatic metastases from colorectal cancer: our experience

M. Varriale, P.L. Bianchi, S. Arcieri, M. Mele, G. Mezzetti, F.M. Di Matteo, N. Peparini, S. Maggi, D. Mascagni and A. Filippini *III Surgical Department, 'La Sapienza' University, Rome, Italy*

Surgical therapy of hepatic metastases from colorectal cancer has shown its impact on survival in selected patients. Moreover the recent increase in radical interventions has made possible the improvement of long-term survival

From January 1985 to July 1995, 342 patients with colorectal cancer were operated on in the III Surgical Department of the University of Rome 'La Sapienza'. Sixty-five of them had hepatic metastases Eighteen of these patients (27 per cent) were operated on Eleven of them (55 per cent) had synchronous metastases and eight (45 per cent) had metachronous ones. Among the patients operated on for synchronous metastases, five are living and four of them are disease-free with a mean survival of 10 months. Among those patients operated on for metachronous disease, four are living and disease-free with a mean survival of 13 months. In all the patients with synchronous disease a tumourectomy was performed. Where there was a metachronous disease two bisegmentectomies, one atypical resection and one right hepatectomy were performed.

It is clear that no conclusion can be drawn from our limited experience. However, it is possible for us to stress the importance of several prognostic factors such as nodal involvement, grading and above all the 'anatomical' performance of the resection that allows a good oncological radicality.

Experience from 62 hepatic resections

A. Veltroni, G. Pangallo, E. Buccianelli, P. Bortolotti and S. Sorce *USL 3 Zona Val di Nievole Presidio Ospedaliero Pescia U.O. Chirurgia, Via C. Battisti, 51017 Pescia, Italy*

From December 1985 to January 1996, the authors have performed 62 hepatic resections. In particular, subsegmentectomy, segmentectomy, right hepatectomy, left hepatectomy and right trisegmentectomy for various pathologies were made. The largest number of cases are metastasis of colorectal cancer, the other cases are hepatic traumas (10 patients), hepatic carcinomas in patients with hepatic cirrhosis, gallbladder cancer, parasitic cysts (Echinococcus) and benign neoplasms (Cavernous hepatic angiomas) The global mortality is 3·2 per cent (two cases). The postoperatory morbidity is 4·8 per cent (three patients with hepatic haematomas drained through the skin by echographic guide) Of the two patients who died, one had a DIC on postoperative day 3 with a multiple organ failure, and one died of portal thrombosis after a right amplified hepatectomy

All operations were made by scissural approach according to Ton That Tung. The survival rate is 29·5 per cent (10 patients) after 3 years and 20 6 per cent (seven patients) after 5 years in patients treated for metastasis of colorectal cancer.

Operative procedures preventing new haemorrhagic episodes by portal hypertension in patients with cirrhosis of the liver

L. Vlad, D. Bindea, C. Mitre and R. Badea *Clinic of Surgery No. 3, University of Medicine Cluj, str. Iasilor, 29, 3400 Cluj, Romania*

Our study deals with the surgical techniques used in cirrhotic patients after an acute episode of variceal bleeding The aim of the operation is the reduction of portal hypertension by means of the portocaval shunt with or without different techniques of oesophago-gastric devascularization The main criterion of patient selection was belonging to the Child A group in which the results of shunting are the best and the risks are few The preoperative check-up every time included the upper digestive endoscopy, hepatic function tests, echo-Doppler examination. We prefer the portocaval shunt with the calibrated Goretex prosthesis (8 or 10 mm) The advantages of this method are prevention of recurrence of variceal bleeding, reduction of encephalopathy rates, no brutal reduction of the portal perfusion to the liver and the operative technique is almost easy In the postoperative follow-up we found the disappearance, or an important reduction, of oesophageal varices and the permeability of the shunt at the echo-Doppler examination We performed this type of shunting in four cases with good results (one patient died after 6 weeks with hepatic insufficiency, despite the permeability of the shunt) We also performed the proximal oeso-gastric devascularization (Hassab operation) in three cases (in two cases it was associated with the splenectomy), and in one patient was associated the portocaval shunt We have been practising these operations in a multidisciplinary team since 1994

Indications and results of liver resection for benign tumours

M. Wolff, J. Kalff, A. Ulrich and A Hirner *Klinik und Poliklinik fur Chirurgie, Rheinische-Friedrich-Wilhelms-Universitat Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany*

Aim: Analysis of long-term results after liver resection for benign lesions. Metanalysis of the pertinent literature in regard to the problem of spontaneous bleeding and malignant transformation.
Methods: Retrospective chart review through a follow-up of the patients operated on by questionnaire, and a review of the literature from 1970 to 1996 by a Medline search in regard to the risk of spontaneous bleeding and malignant transformation of benign liver tumours
Results: Fifty-seven patients underwent liver resection for benign tumours between 1989 and May 1996 Those were 17 haemangiomas, 16 focal nodular hyperplasias, five adenomas, 12 hepatobiliary cystadenomas, and seven miscellaneous Postoperative complication rate was 11 per cent and lethality 0 per cent. Indications were abdominal discomfort in 31/57 patients, undetermined histology (all cystadenomas were mistaken for dysontogenetic cysts preoperatively) in 18/57 patients. Three out of five adenomas turned out to be low-grade HCC in the follow-up. A significant risk of spontaneous bleeding has been reported only for adenomas Iatrogenic bleeding occurs mostly in haemangiomas The risk of malignant transformation has been reported only for cystadenomas and adenomas and occurs, if ever, in <2 per cent.
Conclusion: Liver resection for benign lesions can be carried out with low morbidity and lethality Other causes of abdominal pain should be ruled out carefully. In case of unclear histology, resection should be offered liberally, particularly in patients with low operative risk. However, the risk of bleeding and malignant transformation should not be overestimated

Management of TIPS failures

T. Wróblewski, I. Grzelak, B. Michałowicz, J Pawlak, P. Małkowski, O. Rowiński and S. Polański *Departments of Liver Surgery and Radiology, The Medical University of Warsaw, ul. Banacha 1a, 02 097 Warszawa, Poland*

Aim: Presentation of the cases of TIPS stenosis or occlusion and results of reintervention.
Material and methods: Eighteen transjugular intrahepatic portosystemic shunts (TIPS) were performed in cirrhotic patients with bleeding gastro-oesophageal varices, previously treated by sclerotherapy. In 17 cases the procedure was successful, in one case a technical failure resulted in displacement of a balloon-expandable stent, which migrated to the right ventricle and required emergency surgical intervention. Regular echo-Doppler investigations allowed detection in seven cases stent patency failure.
Results: Early (first 24 h) occlusion of the stent occurred in four patients In all of them an attempt at repair was made (a balloon was introduced by femoral or jugular access). In one case it was successful, the remaining three patients required emergency surgical intervention: two Warren shunts and one non-shunt procedure All patients survived. Late (6–8 months) stent stenosis was found in three cases and was successfully treated by balloon dilatation All patients survived and did not bleed in the follow-up period of 6–12 months
Conclusions: Every patient with TIPS requires systematic echo-Doppler monitoring of the stent patency Occlusion or stenosis is an indication for re-intervention aimed at dilatation or recanalization Early thrombosis may be due to technical error of stent implacement and therefore difficult to repair In case of rebleeding the patient may require emergency surgical treatment

Oesophageal

A comparison of transhiatal and transthoracic resection for oesophageal carcinoma

A. Cariati, M Taviani and E. Cariati *Institute of Anatomia Chirurgica, University of Genoa, Viale Benedetto XV, 10, Genoa, C.A.P. 16132, Italy*

Introduction: Oesophageal carcinoma has a dismal prognosis. In 1980, a review article by Earlam and Cunha-Melo reported a collective operative mortality of 29 per cent [1] In an attempt to lower operative mortality rates for oesophageal cancer resection, Orringer reintroduced in 1978 the transhiatal approach The present study was conducted to analyse retrospectively the postoperative mortality and the long-term results of transthoracic oesophagectomies (TTE) and transhiatal oesophagestomies (THE) performed in a single Institution between 1978 and 1992.

Material and methods: Between 1978 and 1992, 83 patients with oesophageal carcinoma were admitted in a Surgical Institute in Genoa. Among them, 60 patients underwent oesophageal resection by either TTE (n = 48) (40 men, mean age 64 years, 8 women, mean age 61 years) or the THE (n = 12) (10 men, mean age 67 years; 2 women, mean age 63·5 years) The stomach was the preferred organ for the reconstruction (53/60); in five cases of TTE we used the jejunum and in two cases the colon. In the 12 patients that underwent THE the cervical anastomosis was performed at the neck using one interrupted seromuscular layer of propylene or prolene 3/0. Intrathoracic anastomoses of TTE were performed in 13 cases by EEA stapler and in 35 cases by one interrupted seromuscular layer of propylene or prolene 3/0.

Results: The postoperative mortalities of THE and TTE were 16·6 per cent and 20·8 per cent, respectively (P = n.s). Anastomotic leaks occurred in two THE (17 per cent) and in five TTE (10 per cent) (P = n.s.) Colonic interposition was associated with a significant higher mortality than stomach tube reconstruction ($P < 0·05$) Pulmonary complications did not differ between the two groups. Paresis of the recurrent laryngeal nerve was significantly more frequent in THE (4/12) *vs* TTE (0/48). Five-year survival rates were of 18 per cent in THE group and 8 per cent in TTE (P = n.s.).

Conclusions: It is suggested that. (a) THE does not reduce significantly postoperative mortality, (b) long-term survival does not differ between THE and TTE; (c) colonic interposition is associated with a significantly higher mortality than stomach tube reconstruction.

Reference

1 Earlam R, Cunha-Melo J. *Br J Surg* 1980, **67**: 381–390.

Jejunal interposition for peptic stenosis of the oesophagus

U. Della Casa*, M. Picchio*, U. Passarot†, A. Lombardi*, A. Zolovkins‡, P.M. Amodio*, A Paolini† and G. Fegiz* **Ist Department of Surgery, †IVth Department of Surgery, University of Rome, Italy, ‡Department of Surgery, Riga 7th Hospital, Medical Academy, Latvia*

Peptic stenosis is the most frequent complication of gastro-oesophageal reflux disease. In the literature many treatment modalities are proposed and there is a great debate about their optimal use The aim of our study was to analyse the validity of Merendino's oesophagojejunogastroplasty for the treatment of non-dilatable oesophageal peptic stenosis

From 1973 to 1995, 30 patients (16 males and 14 females, mean age 49 years, range 13–73 years), suffering from non-dilatable peptic stenosis, were submitted to oesophagojejunogastroplasty according to Merendino's technique One patient died because of postoperative cardiopulmonary failure (3 3 per cent) A leak at the level of the oesophagojejunal anastomosis occurred in one patient, who was treated with enteral nutrition successfully. In another subject splenectomy was performed after iatrogenic intraoperative injury of the spleen. Minor postoperative complications occurred in six patients (20 per cent).

One year after operation a severe non-dilatable stricture of the oesophagojejunal anastomosis appeared in one patient and was treated with anastomosis resection and reconstruction. We had another case of stenosis of the oesophagojejunal anastomosis, which was treated with perendoscopic dilatation successfully. Another patient was submitted to a partial resection of the interposed redundant jejunal loop 8 years after operation Twenty-seven out of 29 patients (93·1 per cent) were followed up for a mean time of 13 years (range 2–17 years) The results were good in 22 patients (81·5 per cent), fair in three (11·1 per cent) and poor in two (7·4 per cent).

Our study shows that Merendino's oesophagojejunogastroplasty allows us to achieve good results with a reasonable rate of mortality and morbidity in patients with non-dilatable peptic stenosis of the oesophagus.

Comparison of Hill repair and Nissen fundoplication in the treatment of gastro-oesophageal reflux disease

I.M. Civello, G. Brisinda, G. Maria, S. De Fazio and E. Crucitti *Department of Surgery, University Hospital 'Agostino Gemelli', Catholic University, Largo Agostino Gemelli, 8, 00168 Rome, Italy*

Aim: Very few randomized, clinical trials have been conducted to evaluate properly the different surgical techniques and, as a consequence, it is not fully understood how and to what degree the different techniques restore the physiology of the gastro-oesophageal junction In this report we compared the results of Nissen fundoplication with the results of Hill procedure, using a 10-year history of patients with gastro-oesophageal reflux disease (GERD).

Patients and methods: Seventy-two consecutive patients entered the study, 32 (16 males and 16 females, mean age 54·7 years, range 21–79 years) of whom underwent a fundoplication according to Nissen and 40 (15 males and 25 females; mean age 53·2 years, range 19–77 years) a modified Hill operation. In the Nissen Group, intraoperative manometry (IOM) was carried out in all patients; in the Hill Group, the patients were randomized in two groups (A and B), before operation; in 20 of them (Group A), the procedure was associated to IOM.

Results: No postoperative mortality was observed. The results are listed in Table 1.

	Nissen group (per cent)	Hill group (per cent)	P
Morbidity			
Overall	15 6	5·0	n.s
Intraoperative	9 3	2·5	n s
Postoperative	6·2	2·5	n.s
Postoperative symptoms			
Heartburn	21·8	15 0	n s
Regurgitation	12·5	5·0	n s.
Dysphagia	25 0	5·0	0 01
Transdysphagia	25·0	17·5	n.s
Retrosternal pain	9 3	12·5	n s
Gas bloat syndrome	34 3	12·5	0 02
Oesophagitis	21·8	15·0	n.s
Clinical results			
Excellent	65·8	70 0	n.s
Good	21 8	20 0	n s
Fair	6·2	5 0	n.s
Poor	6 2	5 0	n.s.
Manometric results			
LESP (mmHg)	16 8 ± 5 0	14 4 ± 4 5	n s.
LESL (cm)	5·3 ± 0·9	5 2 ± 0 9	n s.
LESIA (cm)	3 1 ± 1 0	3 0 ± 0 4	n.s.

Conclusions: The results of our surgical experience do not differ significantly from the data reported in the international literature: high rate of satisfactory outcomes, extremely low rate of complications, and no operative mortality. We believe that both surgical techniques are effective and well tolerated, and can be properly used in the treatment of GERD, since both techniques carried good clinical results. We think that modified posterior gastroplexy is technically easier than Nissen fundoplication A favourable clinical outcome depends mostly on an adequate LESL and LESIA extension, which could be more efficiently achieved by the use of intraoperative manometry.

Outcome of curative Lewis operation for oesophageal cancer

M.T. Constanda, E. Reis, H Vuilleumier and J -Cl. Givel
Service de chirurgie, CHUV, 1011 Lausanne, Switzerland

Forty-nine patients who underwent an Ivor–Lewis oesophagectomy for cure of squamous cell carcinoma were selected for this analysis All operations took place between 1985 and 1993 in a single teaching hospital. Only cases with resection margins free of tumour and no distant metastasis were included There were 39 men and 10 women, with mean age of 60 years. Thirty-nine patients were heavy smokers and 29 had high alcohol intake Of tumours 65 per cent (32) presented with dysphagia and 10 per cent (5) were found on surveillance. Metachronous and synchronous cancers occurred in eight and two patients, respectively. Radiotherapy or chemotherapy were used preoperatively in 12 patients and postoperatively in three Preoperative work-up predicted resectability in all cases Thirty-day mortality was 6·1 per cent (3) and major or minor complications occurred in half of the patients. Pathological tumour staging (TNM classification) was as follows: stage 0, 3, stage I, 10, stage IIA, 13, stage IIB, 9, stage III, 14 Median survival after curative resections was. stage 0, all survive; stage I, 3·6 years, stage IIA, 1·5 years; stage IIB, 0·4 years and stage III, 1·0 years Lymph-node metastases were found in 49 per cent (24) of specimens. Recurrence of tumour was detected in 24 patients The mean disease-free interval was 12 months.

The Lewis approach carries a significant risk of postoperative pulmonary complications Operative mortality is acceptable in this high-risk group of patients The prognosis after curative resection of oesophageal cancer depends largely on lymph-node status

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Are changes in survival from oesophageal cancer related to changes in the incidence of histological subtype?

K. Dolan, S.J. Walker, R. Sutton and E.M.I. Williams
Department of Surgery, University of Liverpool, Royal Liverpool University Hospital, Liverpool L8 7XP, UK

The incidence of oesophageal carcinoma in the western world is known to be increasing, largely because of increases in adenocarcinoma, but trends in survival have received little attention.

Using data from the Merseyside and Cheshire Cancer Registry from 1974 to 1993, time trends in incidence and survival were examined, including analyses for both squamous and adenocarcinoma histological subtypes

A progressive increase in the incidence of oesophageal carcinoma (9·2–12·6 per 100,000 per year, χ^2, $P < 0{\cdot}001$) was identified, principally attributable to large increases in the incidence of adenocarcinoma that occurred throughout the 20-year period. Significant improvements in 30-day (62–72 per cent), 2-year (8–15 per cent) and 5-year survival (5–9 per cent) were observed over the study period, and were similar for both squamous and adenocarcinoma. The improvements in the 2-year and 5-year survival were more substantial after 1985

These results suggest that the observed changes in survival from oesophageal carcinoma are unlikely to be due to changes in the pattern of incidence of histological subtypes Changes in the management of oesophageal carcinoma, particularly after 1985, should be explored as an alternative explanation for these changes

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Gastro-mediastinal fistula following to a trans-hiatal total oesophagectomy treated by fibrin glue

A. Fimmanò, G. Rondinone, R. Miglio, M. Cioffi and S Masone *School of Medicine, First Department of General Surgery, University of Naples 'Federico II', Naples, Italy*

A 56-year-old male patient underwent an operation for epidermoid carcinoma of the middle third of the oesophagus In the postoperative period, he suffered several complications such as pulmonary embolism, ARDS, inhalation pneumonia and pleural effusions

All these complications came to a spontaneous conservative resolution, but a mediastinal fistula on the transposed gastric tube was present 4 months postoperatively The authors refer about the successful perendoscopic treatment of that complication by some subsequent applications of fibrin glue

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Two-field radical oesophagectomy for adenocarcinoma of the distal oesophagus

U. Fumagalli, S. Bona, R. Rosati, L. Bonavina, A. Ruol, B. Chella and A. Peracchia *Department of General Surgery and Surgical Oncology, University of Milan, IRCCS, Ospedale Policlinico, ICH, Istituto Clinico Humanitas, Milan, Italy*

Surgical treatment of adenocarcinoma of the distal oesophagus is under discussion A wide proximal resection of the oesophagus is mandatory due to the tendency to proximal spread of these neoplasms. A correct abdominal and inferior mediastinal lymphatic dissection is also necessary, due to the pattern of lymphatic spread of the cardial region. The choice of the surgical procedure is between transhiatal oesophagectomy (wide oesophagal resection, abdominal lymphadenectomy and partial inferior mediastinal lymphadenectomy), and the transthoracic *en bloc* oesophagectomy (radical inferior mediastinal lymphadenectomy) We report our results of the surgical treatment of adenocarcinoma of the oesophagus In the period 1980–1995 we observed 314 patients with adenocarcinoma of the distal oesophagus and cardia Most patients were submitted to transthoracic oesophagectomy (TTE. 229 patients), the transhiatal approach (THE. 58 patients) was reserved for patients with contraindication to thoracotomy Operative mortality was 4 5 per cent in the first group, and 6·8 per cent among THE Of the resections 78·3 per cent were classified as R0 Locoregional recurrences were seen more frequently in THE (39 per cent), compared to TTE (26 per cent) The incidence of systemic recurrences was similar in the two groups. Based on these data, in 1993 we started a trial of a wider middle and high mediastinal dissection in order to improve the oncological results after TTE From 1993, 21 consecutive patients with adenocarcinoma of the distal oesophagus and cardia were submitted to TTE with enlarged lymphadenectomy, including right paratracheal and recurrential nodes Operative mortality was 4·7 per cent (one pulmonary embolism). Minor respiratory complications were seen in four patients (19 per cent). There were no recurrent nerve palsies. There was one R1 resection due to neoplastic foci at the proximal resection line. A total of 392 nodes were resected, 155 abdominal and 237 mediastinal. Among these, 157 included nodes within the field of a standard lymphadenectomy, while 80 nodes belonged to the field of an enlarged lymphadenectomy Ninety-nine nodes had metastases (25·3 per cent), 39 of which from the mediastinum (16·5 per cent), 3·8 per cent of superior mediastinal nodes had metastases. These belonged to right paratracheal and sub-aortic nodes All N+ patients had metastases to supra and infra diaphragmatic nodes The patient with R1 resection had a mediastinal recurrence 6 months after surgery Three patients developed systemic metastases After a median follow-up of 16 months, no other locoregional recurrences were observed.

These data confirm the high rate of mediastinal lymphatic metastases in these cancers, and the need to investigate further the role of wide mediastinal lymphadenectomy for these neoplasms

Conservative treatment *vs* Nissen fundoplication in the management of reflux-induced oesophageal strictures

L. Martinez de Haro, P. Parrilla and A. Ortiz *Department of General Surgery, University Hospital Virgen de la Arrixaca, El Palmar, 30120 Murcia, Spain*

Aim: To analyse retrospectively, with a long-term follow-up, the results obtained with conservative treatment and Nissen fundoplication in 87 patients with reflux-induced oesophageal stricture

Patients and methods: Excluded from the study were patients with severe non-dilatable strictures in whom an oesophageal resection was performed and patients in whom a Collis–Nissen procedure was necessary because the surgeon could not obtain a sufficient length of abdominal oesophagus to construct a loose Nissen. The study includes 87 patients. Sixty-one (70 per cent) were men. Their median age was 53 years (range 8–88 years). The strictures were divided into two types: mild (43 cases) when the diameter was >5 mm, the length <5 mm and oesophageal ulcers were absent; and severe (44 cases) when the diameter was <5 mm and/or the length >5 mm and/or ulcers were present. Oesophageal function tests, including oesophageal manometry and 24-h pH monitoring were performed in 48 patients. An abnormal acid reflux rate was documented in 40 patients (83 per cent) with a median percentage of total time with pH <4 of 22 per cent (range 11–65 per cent). The type of treatment depended on the characteristics of the stricture and the general condition of the patient. When the patient was not at any considerable surgical risk (51 cases), our criterion was to indicate Nissen fundoplication as an initial treatment whatever the degree of the stricture. Following this criterion, 45 patients (28 severe and 17 mild) underwent surgical treatment. The remaining 6 (five severe and one mild) refused surgery and were given conservative treatment. Conservative treatment was also used when the patients had a high surgical risk (36 cases) whatever the degree of the stricture (23 mild and 13 severe).

Results: The postoperative mortality rate was 4·4 per cent. Follow-up averaged 7·4 years. Clinical results were satisfactory in 76 per cent of the patients with the non-surgical treatment and in 87 per cent after Nissen fundoplication. The severity of the stricture was significantly related to clinical outcome.

Conclusion: When the patients present a high surgical risk, a conservative attitude should be adopted with the mild forms. Doubts arise in this group of patients when the stricture is severe, since conservative treatment only offers satisfactory results in 55 per cent of patients. Our advice would be to initiate conservative treatment in all patients. Only when no satisfactory result is obtained should surgery be considered, once we have meticulously evaluated the quality of swallowing and surgical risk.

Treatment of the advanced carcinoma of the oesophagus

J.R. Hernández Hernández, R.A. Dominguez Díez, J. García del Caño, F. Martínez Lagares, T. Hernández and V. Núñez Jorge *Servicio de Cirurgía General, Hospital Insular Universitario, Plaza del Dr Pasteur s/n, 35016 Las Palmas, Spain*

Aim: The purpose of this study has been to compare the efficiency of open surgery with endoscopic transtumoural intubation in the treatment of the advanced carcinoma of the oesophagus

Material and methods: From 1993 to 1995 42 patients with advanced carcinoma were treated in our Service of General Surgery. Surgical resection was performed in 21 patients, and endoscopic transtumoural intubation in 21 patients. Clinical evaluation, associated diseases, complementary diagnostic techniques, tumoural location, histopathological study, tumoural staging, quality of life, complementary treatment and survival were evaluated.

Results: The average age of surgically treated patients was 59·7 years, with 17 males and four females. Twenty-one patients presented with dysphagia, 15 weight loss, and nine odinophagia. Fibroscopy was achieved in all of them. The most frequent location of tumour was the middle third (13 patients) epidermoid carcinoma prevailed with 16 patients. Surgical treatment was palliative resection in 18 (85·7 per cent), gastrostomy in two (9·5 per cent), and jejunostomy in one (4·8 per cent). There was one death in postoperative period. The average age of the endoscopic intubation treated group was 66·7 years, with 20 males and one female. Dysphagia in 21 patients, weight loss in 15, and odinophagia in eight patients were the clinical symptoms. Fibroscopy was performed in 21 (100 per cent) patients, the most frequent location of the carcinoma being in the inferior third, $n = 17$ (81 per cent). Epidermoid carcinoma was found in 17 (81 per cent) patients. There was no morbidity and mortality in the endoscopically treated group.

Conclusions: We have found a similar efficacy with these two treatments, although in those patients with disseminated carcinoma or not suitable for palliative resection, endoscopic intubation represents an effective method to achieve control of dysphagia, with no complications and a similar survival

Physiological hiatal repair – is it worthwhile?

B. Kornovski, D. Dobrev, S. Sterev and N. Jelesov
Department of Surgery, Medical University, 55 Marin Drinov Str, 9000 Varna, Bulgaria

In order to eliminate the undesirable side-effects of Nissen fundoplication 96 hiatus hernia and gastro-oesophageal reflux (GER) patients were treated by modified oesophagocruroplasty using the right diaphragmatic crus and partial fundoplication according to Dor technique. The late results were evaluated in a mean follow-up of 3·5 years by means of a questionnaire, X-ray examination and endoscopy. Lower oesophageal sphincter (LES) function was assessed manometrically by a standard station pull-through perfusion technique in 68 patients, 24-h oesophageal and stomach pH-monitoring was performed preoperatively in 80 patients and postoperatively in 40 cases. Excellent and good results were registered with 82 patients (85·4 per cent), GER was abolished permanently in 86 patients (89·6 per cent). LES pressure increased from an average of 9·1 mmHg before operation to 18·6 mmHg postoperatively, LES overall length from 1·5 to 4·0 cm ($P = 0·01$). During the same period 68 patients with GER underwent Nissen fundoplication presenting only 7·4 per cent recurrences (five patients) but an increased incidence of obstructive complications and post-Nissen syndromes (gas bloat, wrap disruption, increased flatus, etc.) which appeared in 13 of them (19·1 per cent). All patients treated by modified crural repair and partial fundoplication demonstrated a preserved ability to belch and vomit, increased flatus was presented in only 2 per cent of them (two patients). Thus the low postoperative morbidity together with the acceptable GER recurrence rate (10·4 per cent, 10 patients) and potential ease of performance have encouraged us to apply the procedure as a routine reconstructive surgical correction of hiatus hernia patients.

Achalasia and carcinoma of the oesophagus: may be a coincidence?

A.M. Maiorana, E. Fiorentino, A. Calí, S. Damiani, H.S. Wu and H.W. Chen *Istituto di Clinica e Fisiopatologia Chirurgica, Via del Vespro 127, 90127 Palermo, Italy*

Different figures regarding the relationship between achalasia and carcinoma of the oesophagus can be found in the literature. Achalasia is often considered as a risk factor. The authors analyse the data collected from the Shanghai Chest Hospital (China) and the surgical pathophysiology of the University of Palermo, both referring centres for oesophageal diseases. The method is a retrospective analysis of achalasic patients who underwent surgical treatment, Heller myotomy plus anti-reflux procedure. The number of cases from the Palermo centre comprise 83 patients (44 males, 39 females) collected from 1980 until 1995. No cases of oesophageal carcinoma have been found during the 6 months–15 years of follow-up.

In the group of patients from the Shanghai Chest Hospital, of 222 patients (136 males, 86 females) collected from 1957 until 1995 only seven developed an oesophageal carcinoma during the 6 months–37 years of follow-up.

According to these data, the authors conclude that carcinoma of the oesophagus in achalasic patients is just a coincidence and no relationship can be found between the two diseases.

Malignant degeneration of Zenker's diverticulum

F. Ochando, R. Gomez, I. Gonzalez-Pinto, C. Jiminez, M. Abradelo, C. Castellón, P. Rey and E. Moreno *Servicio de Cirugía Digestivo y Transplante de Organos Abdominales, Hospital 12 de Octubre, Madrid, Spain*

Introduction: Pharyngo-oesophageal diverticulum or Zenker's diverticulum represents 65 per cent of oesophageal diverticula. Malignant degeneration of its wall is an infrequent complication (0·3–1·5 per cent). Almost every time its diagnostic is performed intraoperatively or less frequently, postoperatively (*in situ* carcinomas). Its prognosis depends directly on an early diagnosis. Factors such as time of evolution of the diverticulum, age, sex, size of the diverticulum, chronic irritation, inability to retain meals, that have been connected with a higher incidence of malignancy.
Material and methods: We have performed a retrospective study on 32 patients who were diagnosed of a Zenker's diverticulum and operated upon in our service between January 1974 and December 1995. We evaluated percentages of malignancy, clinical presentation, preoperative or postoperative diagnosis and the treatment.
Results: From 32 patients, in just one case was the diagnosis of epidermoid carcinoma made. This represents 3·1 per cent. The patient was a 60-year-old male; and his clinical signs were cervical progressive dysphagia and regurgitations of more than 15 years' evolution. In the last few months these symptoms had suddenly worsened. He just could tolerate liquids. The preoperative diagnosis was not made, even barium gastro-oesophageal transit and endoscopic study were performed. Surgical technique as diverticulectomy: the tumour was localized in diverticular body and did not infiltrate the neck of the diverticulum. The histopathological diagnostic was epidermoid carcinoma. The patient received radiotherapy. He died after 18 months.
Conclusions: Early diagnosis is important in view of the bad prognosis of this kind of tumour and the frequency of early recidives. The presence of a carcinoma must be suspected in all the patients with Zenker's diverticulum and worsening of his symptoms, more frequently if the patient is a male between 50 and 60 years old. A barium pharyngo-oesophageal transit and an endoscopic study must be performed, which allows us to take samples for biopsy. Simple diverticulectomy can be enough in those tumour which do not reach the neck of the diverticulum. Radiotherapy treatment must always be performed. We recommend surgical treatment for all symptomatic Zenker's diverticula.

Cervical oesophagogastric anastomosis with the biofragmentable anastomosis ring

T. Oláh, V. Szendrényi, B. Szalay and Á. Balogh
Department of Surgery, Albert Szent-Györgyi Medical University, Szeged, Hungary

The practice of performing sutureless anastomoses with the Valtrac bioabsorbable anastomosis ring (BAR, Davis and Geck, USA) has been shown to be a safe and efficient technique for intra-abdominal large- and small-bowel anastomoses. Because of its fragmentability and applicability, the BAR offers the advantages of a circular stapler, without needing additional enterotomy. In February 1996, one male and one female patient, aged 48 and 61 years, underwent transthoracic oesophagectomy for squamous cell carcinoma of the thoracic oesophagus. The gastric tube was made mechanically, and the end-to-side cervical oesophagogastric anastomoses were performed with a 25-mm BAR with a gap of 2·5 mm in both cases. There were no intraoperative complications, and the postoperative course was similarly uneventful. The integrity of the anastomosis was checked by an oesophageal X-ray with gastrografin 8 days postoperatively. There was no evidence of leakage, and a liquid diet was started. The radiological fragmentation of the BAR was noted on postoperative day 21 or 27. Our initial experience with use of the BAR in performing cervical oesophagogastric anastomosis after oesophagectomy indicated that, if the gastric tube is long enough, it is an easy procedure. However, we need a greater number of patients before an evaluation of the safety of the BAR in oesophageal surgery.

The effect of coeliac ganglion blockade on the microcirculation of the stomach in the dog

V. Szendrényi*, T. Oláh*, J. Fogas†, M. Boros‡ and K.T. Barna§ **Department of Surgery, †Medical Intensive Care Unit, ‡Institute of Experimental Surgery, §Blood Transfusion Center, Albert Szent-Gyorgyi Medical University, Szeged, Hungary*

Introduction: Epidural anaesthesia has analgesic and local sympatholytic effects (dilatation of arterioles and increased blood flow of tissues), which can contribute to the better healing of the oesophageal anastomosis.
Aim: The arteriolar dilatation in the stomach was studied during coeliac ganglion blockade to establish whether the blockade can prevent worsening of the circulation of the stomach resected according to Akyama.
Method: Epidural anaesthesia was simulated by infiltration of the coeliac ganglion with 0·5 per cent ml marcaine solution in three groups of anaesthetized dogs. The first ($n = 6$) was the control group, only ganglion blockade was performed, and not gastric resection. In the second group ($n = 6$) the blockade was performed before, and in the third group ($n = 6$) at the end of surgery. The vasoconstriction-dilatation and the oxygen saturation of the arterial blood in the wall of the stomach were measured with a volumen-plethysmograph (Datex). Intramucosal pH was monitored for observation of the microcirculation of the gastric wall with a balloon probe (Tonomitor). The degree of hypoxaemic damage of the gastric mucosa was classified on the Chiu scale at the histological examination.
Results: In the controls the coeliac ganglion blockade resulted in the arterial inflow increasing up to 1·5–2-fold without intramucosal pH or morphological changes. The arterial inflow decreased slightly or was unchanged during the operations performed under sympathetic blockade protection with an intramucosal pH decrease and discrete morphological changes; a very strong regional vasoconstriction, a fall in pH and destructive morphological changes were observed without infiltration.
Conclusions: The regional vasodilatation and the increasing oxygen supply attributed to epidural anaesthesia are not accompanied by a definite improvement in the microcirculation of the tissues in all cases, but they prevent serious damage to the tissues. The sympathetic blockade works against the splanchnic vasoconstriction caused by general anaesthesia, and hence contributes to the success of surgery.

Comparative value of endoscopic and histologic study of the oesophageal mucosa and 24-h pH-metry in patients operated on for GERD

G. Wallner, P. Misiuna, D. Chibowski and A. Sory *2nd Department of General Surgery, Department of Pathology, Medical Academy, Lublin, Poland*

The aim of this prospective study was to evaluate the pathological GERD changes in oesophageal mucosa comparing endoscopy and biopsy results with 24-h pH-metry. Fifty-three patients with GERD were evaluated before and after the Nissen–Rossetti fundoplication with X-ray, oesophagoscopy, biopsy, 24-h pH-metry and manometry. The mean follow-up period was 18 months. Statistical significance was determined using

Wilcoxon test, with P-values <0·05 considered as significant. Microscopic specimens of the oesophageal mucosa were collected from the anterior and posterior wall of the oesophagus 3, 5 and 10 cm above endoscopically considered GE-junction Complete postoperative relief of GERD symptoms obtained in 83 per cent patients ($P < 0{\cdot}005$), and GE-junction restoration in X-ray (85·2 per cent, $P < 0{\cdot}001$), was confirmed by healing of mucosal lesions in endoscopy (81·1 per cent, $P < 0{\cdot}005$)· 24-h pH measurement and manometry revealed a significant decrease of pathological reflux (DeMeester score 21·5 ± 12 19 *vs* 3·43 ± 5·22, $P < 0{\cdot}001$), with normalization of LES resting pressure (6·8 *vs* 18·2 mmHg, $P < 0{\cdot}0005$), improvement of the complete peristaltic spasms (17·8 *vs* 41·4 per cent, $P < 0{\cdot}002$) and peristaltic effectiveness (15·5 *vs* 33·5 per cent, $P = 0{\cdot}003$). Biopsy study revealed healing of microscopic lesions in 54·5 per cent patients, P = n.s., progression in 12·6 per cent and 32·7 per cent persisted without any postoperative changes independently of postoperative improvement of other diagnostic parameters The most significant regression to normal mucosa of squamous oesophagitis/hyperplasia was observed in patients with CLE (86·7 per cent, $P < 0{\cdot}01$). However, the incidence of histopathological lesions observed after the operation was still unexpectedly high 81·1–67·9 per cent patients depending on the level of biopsy in the oesophagus Biopsy as well as endoscopy confirmed the most severe lesions of the oesophageal mucosa with unsatisfactory 24-h pH parameters directly over GE-junction. Patients with CLE had significantly worse results of 24-h pH-metry in comparison with squamous oesophagitis and normal mucosa in all levels of microscopic examination Persisting pathology or progression of mucosal lesions after the operation were connected with deterioration of 24-h pH parameters Causality between the severity of mucosal lesions in endoscopy or microscopic study and the grade of pathological reflux in 24-h pH measurement was proved in evaluation of DeMeester score, as well as in total, upright and supine period pH < 0·4 analysis

Oncology

Multiple primary malignancies (MPM): considerations on 75 cases

N. Angelescu, T. Burcoş, D Cristian, C. Dimitriu,
M. Bărbulescu and C. Mihai *Colţea Hospital, Surgical Department, Bucharest, Romania*

Aim: Showing out the incidence of multiple primary malignancies (MPM) and the predisposing factors of their development

Material and method: Between 1984 and 1994, 75 patients with MPM (63 women and 12 men, 25–87 years old) underwent surgery There were synchronous ones in 33 patients and metachronous in 42 In 28 patients with synchronous MPM the diagnosis was established at first admission, and in five, 2–18 months after the first operation In the patients with metachronous MPM, the second tumour become evident in 2–19 years.

We encountered the associations shown in Table 1.

Primary cancer	Synchronous/Metachronous								
	Breast	Colon	Stomach	Rectum	Ovary	Uterus	Pancreas	Gallbladder	Other
Breast	2/11	0/1	—	—	1/3	1/3	0/2	—	1/2
Colon	—	7/3	—	2/1	—	—	3/0	—	0/1
Stomach	—	—	—	—	—	—	1/1	1/0	—
Rectum	—	—	—	—	—	—	—	—	1/2
Ovary	—	0/2	—	0/2	—	—	—	—	2/0
Uterus	—	0/1	—	0/1	5/2	1/0	1/1	—	1/2
Other	—	—	—	—	—	—	—	—	1/1

The histopathological aspects were of carcinomas in 67 and sarcomas in seven patients The surgical approach to the MPM syndrome was used in 24 simultaneous operations (22 radicals) and seven successive operations. For the metachronous MPM all 42 primary operations were radical ones, but for the second localizations only 19 were radical. Sixty-one patients underwent adjuvant therapy (radio ± chemotherapy) postoperatively. The incriminated aetiopathogenic factors were· hormonal dysfunction, age over 40 years, adjuvant therapy

Conclusions: Synchronous and metachronous MPM are facilitated by factors dominated by immunological depression. The radical treatment is the goal for all localizations (preferably simultaneous for the synchronous MPM). The periodical follow-up of the patient with a neoplasia is mandatory for the rest of his/her life.

Physicians' attitude to advanced or relapsed rectal carcinoma

S. Arnaud, G. Houvenaeghel and J.P. Moatti *Institut Paoli-Calmettes, 232 Bd Sainte Marguerite, 13273 Marseille, France*

We are currently investigating therapeutic attitudes to advanced or relapsed rectal carcinoma in France Amongst our aims is the determination of the physician-based factors which influence therapeutic choices. This study is addressed to various specialized physicians. gastroenterologists, oncological physicians, radiotherapists and digestive surgeons, all involved in rectal carcinoma treatment A questionnaire was sent that included an inquiry form and three clinical cases to a representative sample of 1000 physicians The first clinical case deals with a patient bearing a T3N0 tumour The second one concerns a rectal carcinoma with rectovaginal fistula. The third one deals with locoregional relapse 5 years after a previous rectal carcinoma treatment. Preliminary results from the preinvestigation concern 39 physicians including seven gastroenterologists, five oncological physicians, nine radiotherapists, 11 digestive and general surgeons, six other surgeons The sample covered a majority of men (36 men, two women, one unknown), the average age is 47 years old

In the first clinical case, dealing with the type of therapeutic choices, six physicians would take their decision alone, one physician would send his patient to a specialized colleague, seven physicians solicit the advice of a colleague and 25 take their decision during a multidisciplinary meeting In 26 cases, radiotherapy-surgery association is proposed, in 13 cases, radiotherapy-surgery-chemotherapy is proposed.

For the second clinical case, only one physician would take his decision alone, two physicians would send their patients to specialized colleagues Ten of them would call for a colleague's advice, 26 of them would take their decision during a multidisciplinary meeting. The association of surgery-radiotherapy and/or chemotherapy is chosen by 36 physicians and the surgery and/or chemotherapy is chosen by three physicians

In the last clinical case, one physician would take his decision alone, nine with a colleague, 22 during a multidisciplinary meeting. Twenty-nine physicians prefer the radiotherapy-surgery and/or chemotherapy association, two physicians prefer the radiotherapy-chemotherapy association and one chooses surgery alone.

This original approach for therapeutic attitudes has not yet been done for the subject in which we are interested. One of the final interests is the preparation and the realization of multicentric study involving concerned physicians.

Long-term results in stage II and II(a+b), breast carcinoma after using different therapeutical regimens

F Badulescu, A. Dragusin, L. Pirvulescu, M Danciulescu and L. Pop *Oncology Department, Clinic Hospital No. 1, Faculty of Medicine, University of Craiova, 1100, Romania*

Aim: The evaluation of the results of a study begun in 1985 that enrolled patients with breast carcinoma-stage II and III(a+b)

Material: We have followed dynamically 70 patients; half of them in premenopausal status and half in postmenopasual status (earlier or later), with ages between 28 and 60 years, most of them were overweight, 35 refused surgery at any time; the entire group of study has presented more than three risk factors The diagnosis was made up by 'T' and 'N'-elements The malignancy was established by histopathological extempo-raneum in operated patients and by fine-needle aspiration with cytological examination or by cytological examinations of the ulcerated lesion in stage IIIb

Results: We have achieved. (a) undifferentiated evolution in the first 2 years of treatment (for operated and unoperated); (b) undifferentiated evolution after 2 years, also in postmenopausal patients—the unoperated patients were treated by the association of CT + RT (9–12 sequences-CMF, 5500 rad for every field) and hormonotherapy with tamoxifen 20 mg/day; (c) a differentiated evolution in premenopausal patients—the unoperated showing recurrence after 16–18 months, imposing the repeat of CT and a bigger dose of RT

Conclusions: (a) The invasive forms have a differentiated evolution with or without surgery; which is favourable in postmenopausal, and which has a recurrent potential in premenopausal patients, the younger the patient the greater this is (b) Without surgery, considering breast carcinoma as a systemic disease, from the moment of invasion—the association of CT + RT keeps the mammary gland with a good psychological effect; (c) the result of conservative surgery is a histoprognostic factor, because it offers the necessary elements for further therapy, e g. systemic treatment beginning with T2, preventing in this way the possible recurrence and metastasises (the most involved being the bone)

Stage I non-small-cell lung carcinoma: lobectomy *vs* segmentectomy

S. Blanco, A. Gómez, F. Hernando, J. Calatayud,
S. Ochagavía, R Cantero, A.J. Torres and J.L. Balibrea *II Department of Surgery, Hospital Universitario San Carlos, C/ Martín Lagos s/n, 28040 Madrid, Spain*

Introduction: There is controversy between the performance of lobectomy and other more conservative resections such as segmentectomies in the surgical treatment of non small-cell lung cancer (NSCLC) with curative intentions, specially in stage I Our aim was to compare the results obtained after lobectomy with those obtained after segmentectomy resection in stage I NSCLC patients.

Patients and methods: One hundred and sixty patients diagnosed and treated in our service from January 1982 to December 1995 from stage I NSCLC have been involved in the study, having excluded those cases treated with adjuvant chemotherapy or radiotherapy They were divided according to the type of resection into two groups. A· lobectomy, and B. segmental resection Their mean age was 63·5 years (range 24–84 years) Sex distribution was males 143 (89·3 per cent) and women 17 (10 6 per cent). The age, sex, the pathological type, the morbimortality, the global survival and disease-free interval were analysed.

Results: We have carried out 101 lobectomies (63 7 per cent) and 59 segmentectomies (36·8 per cent) Both groups have homogeneous results in terms of age, sex and histopathological subtype Postoperative complications appeared in 25 patients of the Group A (24·7 per cent) and in 14 patients of Group B (23·7 per cent), and postoperative mortality in seven cases of Group A (6·9 per cent) and in three of Group B (5 per cent) We have detected a greater percentage of recurrence in Group B patients (15 cases· 27·2 per cent) than in those treated with lobectomy (15 cases. 16·5 per cent), 11 (20 per cent) and 10 (11 per cent) respectively due to locoregional relapse. These differences were not statistically significant. The global survival, excluding the cases lost during the surveillance and the postoperatory mortality have been 73 per cent at 2 years and 58 per cent at 5 years, without significant differences were comparing both groups (Group A· 72·6 per cent and 60 per cent), (Group B· 74 2 per cent and 56 per cent).

Conclusions: Segmentary resection in stage I NSCLC patients is penalized with a greater percentage of recurrence of the illness than lobectomy, especially locoregional relapse However, there is no significant difference in survival and disease-free interval with similar morbimortality rates

Validity of Dukes classification for gastric cancer

L. Bruno*, G Nesi†, V. Boddi‡, P.C Cecchi, P. Bechi and C. Cortesini **Istituto di Clinica Chirurgica Generale, D.C., †Istituto di Anatomia Patologica, ‡Istituto di Patologia Generale, Università di Firenze, Italy*

Aim: Dukes classification for colorectal cancer is simple, highly reproducible and correlates well with prognosis. Our study investigated whether the criteria of this staging system, applied to gastric carcinoma (GC), allowed a better prognostic stratification of patients and thus a more effective treatment.

Patients and methods: Between January 1986 and December 1995, 288 out of 361 consecutive patients with GC were resected at our institute (resectability rate 79·8 per cent). The patients were then stratified according to TNM, Japanese Research Society for Gastric Cancer (JRSGC) and Dukes classification Dukes C cases were subdivided depending on the depth of tumour invasion, the number and site of positive lymph nodes (LN) The cumulative survival rates were calculated using the Kaplan–Meier method and survival curves were tested using the Cox method.

Results: According to TNM system there were 89 patients at stage I, 40 patients at stage II, 47 patients at stage IIIa, 46 patients at stage IIIb and 66 patients at stage IV, according to the JRSGC classification there were 81 patients at stage I, 47 at stage II, 92 at stage III and 68 at stage IV. Following Dukes classification 81 patients were at stage A, 22 at stage B, 185 at stage C subdivided into 138 with serosal involvement and 47 without; 104 with up to six positive LN and 81 with more than six positive LN, 75 with N1 and 110 with N2 Analysing the survival curves each classification showed a close correlation with prognosis ($P < 0{\cdot}001$).

Conclusions: With regard to stratification of high-risk patients, Dukes classification does not seem to have advantages over TNM and JRSGC staging systems This is likely to be due to the fact that in western countries the percentage of patients with positive LN is significantly higher in GC than in colorectal cancer. However, the number of positive LN is a well-known prognostic indicator for GC and the results of the log-rank test demonstrate that the prognostic value of Dukes classification is strengthened when Dukes C cases are subdivided according to the number of positive LN

Prognostic factors in resected gastric cancer

F. Sánchez-Bueno, J.A Garcia-Marcilla, F. Aranda, J.M. Rodriguez, J. S Garrido, L. Carrasco, F. Martinez, P. Ramirez and P. Parrilla *Department of General Surgery, University Hospital 'Virgen de la Arrixaca', 30120 Murcia, Spain*

The aim is to analyse the survival rate of a series of 297 patients treated in our department for gastric adenocarcinoma, in whom the tumour was able to be resected, and relate it to a series of factors to determine their influence on the prognosis of this neoplasia.

Materials and methods: Over a period of 15 years our department admitted 504 patients with gastric adenocarcinoma. Of the 504 cases, 443 (87 9 per cent) underwent surgical operation and in 321 (63·7 per cent) it was possible to remove the tumour. Of the 321 resected cases, 24 died (7·2 per cent) in the immediate postoperative period (first 30 days), the remaining 297 were discharged from hospital and are the object of our study. Mean age was 61 9 years (range: 30–88 years); 195 (65·6 per cent) were males and 102 (34·4 per cent) females. With regard to treatment, 208 cases (70 per cent) received a subtotal gastrectomy, 78 cases (26·3 per cent) a total gastrectomy of necessity and the remaining 11 (3·7 per cent) a proximal gastrectomy In the survival analysis we analysed. (a) clinical variables (sex, age, evolution time and clinical data); (b) treatment-related variables, and (c) anatomopathological variables (tumour site, macroscopic variety, degree of cellular differentiation, tumour size and stage.

Results: The overall survival rate of our series was 35·7 per cent at 5 years and 21·9 per cent at 10 years In the univariate analysis the survival-related factors were weight loss ($P < 0{\cdot}05$), abdominal mass ($P < 0{\cdot}05$), dysphagia ($P < 0{\cdot}01$), type of gastrectomy (subtotal gastrectomy *vs* total gastrectomy), intention of the resection (curative resection *vs* palliative resection) ($P < 0{\cdot}001$), tumour site (tumours located in the distal third and/or middle third *vs* proximal third) ($P < 0{\cdot}001$), size of the neoplasia (less than 3 cm) ($P < 0{\cdot}001$), degree of gastric wall invasion ($P < 0{\cdot}001$), degree of lymph node invasion ($P < 0{\cdot}001$) and stage of the neoplasia ($P < 0{\cdot}001$) The rest of the variables analysed had no significant influence. In the multivariate analysis we found that degree of gastric wall invasion, lymph node invasion and intention of the resection were the only independent prognostic variables.

Conclusions: There are only three variables in our experience with prognostic influence in resected gastric cancer

Improved survival in resection of pulmonary metastases in patients with colorectal cancer

M. Cappello*, J.L. Jansens*, Y. Sokolow*, J. Closset†, P. de Francquen*, M. Gelin† and P. Rocmans* **Department of Thoracic Surgery and †Medicosurgical Department of Gastroenterology, Hospital Erasme, Université Libre de Bruxelles, 808, Route de Lennik 1070 Brussels, Belgium*

Lung and liver are the two most common sites of visceral metastases from the colorectal carcinoma These metastases occur in about 10 per cent of patients but the poor long-term survival of unresected metastases (median survival 11 months) justifies a more aggressive treatment. In this retrospective study, the results of 61 hepatic and 18 pulmonary metastasectomies were compared The number of resected metastases ranges from one to seven for liver and one to three for lung For pulmonary metastasectomies there was no mortality and no significant morbidity. However, for liver metastasectomies surgical mortality was 1·6 per cent (1/61), and major morbidity was 36 per cent (22/61): 21 per cent medical complications (13/61), 14 per cent surgical complications (9/61). We observed the same selection criteria: number of metastases (single *vs* multiple), disease-free interval (longer in lung metastases) and complete resection Five-year survival rates were respectively 22 per cent and 51 per cent for hepatic and pulmonary metastasectomies Therefore, we can conclude that isolated lung metastases of colorectal carcinoma represent a less aggressive form of the disease than isolated liver metastases.

Optimal dose of garlic to inhibit the growth of colorectal cancer

J.-Y. Cheng, J.-C. Lin and C.-L. Meng *Division of Colorectal Surgery, Department of Surgery, TRI-Service of General Hospital, Taipei, Taiwan, China*

Aim: Garlic has been found to prevent colorectal cancer This study was the first report to investigate the optimal dose of garlic during long-term feeding.
Method: A total of 240 male Sprague–Dawley rats were grouped and fed with either a basal or a garlic diet of different concentrations, and some groups were subcutaneously injected with 1,2-dimethylhydrazine (DMH) 20 mg/kg once a week for 20 weeks
Results: The incidence of colorectal tumour was significantly decreased in the groups fed with 2·5 per cent, 5 per cent, and 10 per cent garlic diet ($P < 0{\cdot}001$) There was no distinct difference among these concentration ($P > 0{\cdot}05$). Therefore, the minimal optimal dose of garlic to inhibit colorectal cancer was 2·5 per cent. The equivalent dose of this concentration in human is 4·76 g/m^2 body surface/day. In a therapeutic study, the tumour-inducing interval in nude mice subcutaneously injected with colon cancer cells (CC-M2) was prolonged by a 2·5 per cent garlic diet ($P < 0{\cdot}01$). Thus smaller tumour volume and longer survival time were found in the garlic group than in the controls ($P < 0{\cdot}01$) However, the growth rate of tumours was not markedly inhibited by garlic. All rats finally died within 18 weeks
Conclusion: This study suggested that a 2·5 per cent garlic dose (approximately 10 gm/day in a 80 kg human) may be used mainly as an inhibitor to prevent colon cancers and improve survival time.

Detection of malignant lesions in human colon by digital imaging of laser induced autofluorescence

B.W. Chwirot, W. Jędrzejczyk, S. Chwirot, Z. Michniewicz, A. Raczyńska and M Modrak *Interdisciplinary Group of Optical Methods of Early Detection of Cancer, Copernicus University, Toruń, Poland*

We have carried out studies on the possibility of using digital imaging of the laser-induced autofluorescence (AFL) of colorectal tissues for a detection of premalignant and malignant lesions. Ultraviolet light of He-Cd laser was used for the excitation and the images of the AFL were recorded *in vitro* in six regions of a visible spectrum using a cooled CCD camera designed for low-light applications Two hundred and thirty-three areas of 50 tissue specimens received by surgical procedure were examined. It was found that in the spectral bands investigated the malignant tissues generally showed lower intensity of the AFL than normal mucosa but inflammation of mucosa characterized of higher intensity of AFL than normal mucosa. The ratio of the intensity of the AFL of normal and abnormal mucosa seems to be a sensitive parameter for a discrimination of carcinomas from normal colorectal mucosa.

The method is less sensitive in detecting adenomatous polyps, independently of a degree of dysplasia.

Early gastric cancer today

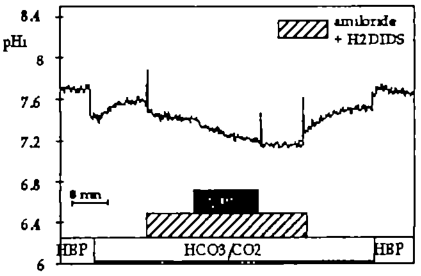
B. Flor Civera, J.M. Muñoz Camarena, J Martin Arévalo, B Flor Lorente, J. Willat, R. Martí Obiol, V. Martí Martí and S. Lledó Matoses *Hospital Clínico Universitario de Valencia, Avda. Blasco Ibáñez 17, 46010 Valencia, Spain*

We show the results of a 22-year multifactorial analysis of the management of early gastric cancer in the Clinical Hospital in Valencia
Method: Over the 22-year period from 1974 to 1996, 1184 patients were admitted to our Hospital with the diagnosis of gastric cancer, 96 of whom were diagnosed with early gastric cancer. The factors analysed were sex, median time of symptoms, initial symptom, macroscopic features, histopathology (Lauren Classification), type of surgery, VISICK Index, survival and morbidity Follow-up ranged from 1 to 200 months
Results: Fifty-three men and 43 women of median age 61 years were operated on electively The most frequent presentations were those of ulcer and non-ulcer dyspepsia with gastric haemorrhage (71 per cent cases) The initial symptom was epigastric pain in 62·7 per cent of cases The median time of symptomatology was 31·12 months The most frequent macroscopic feature was pediculate polyp (type I and type IIa) in 18·8 per cent of cases The most frequent location was the lesser gastric curvature (65·3 per cent). The operations performed were: partial gastrectomy (1·3 per cent), subtotal gastrectomy (61·3 per cent), total gastrectomy (36·1 per cent) The types of gastrojejunostomy (30·6 per cent), Billroth II operation (24 per cent), oesophagojejunostomy (24 per cent) The histological features were of intestinal type in 50·6 per cent of cases and diffuse type in 42 per cent. The median survival was 37·45 months.
Conclusions: The diagnosis of early gastric cancer is important since the survival rate after gastrectomy is high with a good quality of postoperative life, and so a complete study of epigastric pain of long duration is necessary. We consider total gastrectomy an adequate surgical procedure except in those cases where the localization is purely antral and without lymph node metastasis

Multiple drug resistance: chemomodifiers verapamil, cyclosporin A and tamoxifen decrease pHi in human colon cancer cells

E. Cosentini, G. Hamilton, J. Zacherl, G. Bischof, B Teleky, M. Riegler and E. Wenzl *University Clinic of Surgery, A-1090 Vienna, Austria*

Reduced chemosensitivity of sarcomas and carcinomas in response to chemotherapeutic drugs such as vinca alkaloids, podophyllotoxins and anthracyclines, is mediated by the mdr-1-encoded ATPase-linked-P-glycoprotein drug efflux pump By reversing the MDR-phenotype with verapamil (VPL), cyclosporin A (CsA), certain hormones and other drugs an increase of intracellular drug accumulation can be achieved *in vitro* Such a resistance-modification may be due to different mechanisms such as direct binding to P-glycoprotein, competitive inhibition to drug transport (VPL) and non-specific membrane alterations by lipophilic drugs In our study we investigated the effect of VPM, CsA and tamoxifen (TMX) on pHi in different colon carcinoma cell lines (CaCo-2, HT-29, SW 620).
Methods: pHi was recorded by spectrofluorimetric monitoring of the pH-sensitive, fluorescent dye BCECF. Dye loaded cells were incubated either in Ringer-HEPES or Ringer-HCO$_3$ buffered solution (pHo = 7·4, 25 °C) and VPL (1 µM), TMX (2 µM) and CsA (1 µg/ml) were added Calibration in terms of pHi was performed according to the high [K] Nigericin method. Within this concentration range resistance modification was demonstrated in chemosensitivity tests using doxorubicin in a thymidine incorporation assay
Results: Addition of VPL, CsA and TMX led to a reversible and dose-dependent decrease in pHi (0·1–0·3 units) within 10 min for all colon carcinoma cell lines Inhibition of the Na/H exchanger and the HCO$_3$-dependent transport systems with amiloride and H2DIDS showed that VPL, CsA and TMX do not interfere with these pHi-regulating mechanisms, pointing to other membrane-based mechanisms



Conclusion: Since colon carcinoma cells exhibit a higher resting pHi compared to normal colon crypt cells it is possible that intracellular acidification increases the sensitivity of the cell lines to chemotherapeutic agents. This is supported by a minimal cell survival at lower pHi in response to doxorubicin in the SW 620 cell line under tissue culture conditions at 15–20 mM HCO_3/5 per cent CO_2 Alteration of pHi-regulating mechanisms with specific ion channel inhibitors may enhance the modulating effect of MDR-targeted drugs and contribute to increased drug sensitivity.

CDDP hepatic arterial infusion (HAI) and i.v. 5-FU chemotherapy for unresectable colorectal liver metastases

M. Cosimelli*, A. Callopoli*, M Tedesco*, D. Giannarelli*, C. Frigieri*, E. Cortesi†, P. Di Tora‡, L. Capussotti§ and D. Civalleri¶ *Regina Elena Cancer Institute, Rome, †University of Rome, ‡University of Palermo, §Mauriziano Hospital, Torino, ¶University of Genoa, Italy

Aim: The aim of the present study was to evaluate the effectiveness of the combination CDDP HAI and bolus i.v 5-FU in terms of response and survival rates, in comparison to results traditionally obtained with FUdR HAI

Materials and methods: One hundred and twenty-three patients at stage II and III according to Gennari's classification were included in a phase II randomized multicentric clinical trial. All the cases were randomized in two different modalities to receive CDDP (bolus *vs* chronic HAI) 24 mg/m^2/day and bolus i.v. 5-FU 500 mg/m^2/day both per 5 every 28 days.

Results: Out of 98 evaluable patients objective responses were 51 (52 per cent) with no significant differences between the two groups. Complete responders were 17 (17·3 per cent). As far as toxicity regarded, haematological events and nausea/vomiting were the most observed ones (53 per cent and 79 per cent, respectively) but only 26·4 per cent and 30·4 per cent were $G \geq$ three events. Minor toxicity were pain, gastrointestinal, fever and neurological peripheral (ranging from 15 per cent to 26 per cent). Group B (CDDP chronic infusion) experienced a lower number of toxic events in comparison with Group A (157 *vs* 120). The 5-year overall survival was 19 per cent, without statistical difference between the two Groups. Complete and partial responders displayed a longer survival than patients with stable or progressing disease (25 per cent *vs* 0 per cent at 5 years, $P = 0{\cdot}002$).

Conclusions: The response and survival rates were satisfactory even if the toxicity was relatively high, affecting the quality of life. Particularly, the complete responders had a long-term survival, which is unusual in patients with unresectable colorectal liver metastases

Partially supported by Project A.I.R.C. n° 95/30/R/42 and Project C N R A.C.R O n° 9500482PF39.

Proliferating cell nuclear antigen expression (PCNA) and flow-cytometric studies in ampullary carcinoma

A. Crucitti, R. Masetti, R. Coppola, N. Maggiano*, C. Breccia, P. Magistrelli, G. Nuzzo and A. Picciocchi Department of Surgery and Department of Pathology*, Catholic University, Rome, Italy

In the period 1967–1995, 64 patients with cancer of the ampulla of Vater were treated at our Department In the present study, PCNA expression, DNA-ploidy and S-phase were retrospectively determined in 15 formalin-fixed, paraffin-embedded specimens and were then correlated with other clinicopathological features (T, N and stage of the disease) to evaluate their prognostic relevance

A statistically significant correlation was shown between PCNA-positive rate and both the size of the tumour ($P = 0{\cdot}01$) and the stage of the disease ($P = 0{\cdot}03$) Patients with cancers invading the pancreatic parenchyma (T3–T4) had PCNA-positive rates higher than patients without invasion of the pancreatic tissue (ANOVA method, Schuffe-test = 5·28). Patients with stage II tumours showed higher PCNA-positive rates in comparison to patients with stage I disease (ANOVA method, Sheffer-test = 3·42) No statistically significant correlation was observed between PCNA-positive rates and lymphonodal status or grading. Flow-cytometric analysis revealed diploid-DNA content in 10 patients and aneuploid-DNA content in five Patients with diploid-DNA content had a median survival time of 51 months as compared to 18 months in the aneuploid group. Univariate analysis also showed a statistically significant correlation between S-phase and PCNA-positive rate ($P = 0{\cdot}04$). No significant correlation was observed between PCNA-positive rate and DNA-ploidy The above results, as those of other authors[1,2] suggest that immunochemical and flow-cytometrical characteristics could be of prognostic relevance in patients with ampullary carcinoma. More data are needed to assess their exact significance in the evaluation of tumour progression and their usefulness in therapeutical planning for these patients.

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Differences in p53 expression, histopathology and clinical features between mucinous and non-mucinous colorectal adenocarcinomas

M. Diez, J.M. Enríquez, E. Tobaruelña, J. Camuñas, P. Dominguez, T. Ratia, A. Gurérrez, A. M. Duce, A. Ruiz and J. Granell General Surgery, Hospital Príncipe de Asturias, Alcalá de Henares, 28005 Madrid, Spain

Aim: To assess the biological and clinical significance of histological typing of colorectal adenocarcinomas

Patients and methods: Retrospective analysis of 140 colorectal adenocarcinomas 22 (15 per cent) mucinous (MC), and 118 (85 per cent) non-mucinous (non-MC) Both types of tumours were compared with respect to clinical characteristics, p53 oncogene protein expression (CM1 antiserum), proliferative cell nuclear antigen (PCNA) labelling index, DNA ploidy (by flow-cytometry), and histopathological features of the malignant phenotype Paraffin-embedded material was used for pathological studies.

Results: Both types of tumours differed in incidence, localization, morphology, and pattern of genetic lesion MC patients were significantly younger than non-M (57 ± 12 years *vs* 65 ± 17 years) ($P = 0{\cdot}05$). MC were more frequently located in right colon than non-M carcinomas (63 per cent *vs* 28 per cent) ($P < 0{\cdot}001$) p53 positive nuclear staining was significantly less frequent in mucinous carcinoma (8 cases; 36 per cent) than in non-M (69 patients, 58 per cent) ($P = 0{\cdot}02$) All MC showed infiltration of the bowel wall involving the subserosa (50 per cent in non-M) ($P = 0{\cdot}02$), and in all cases the tumour margin showed an infiltrative behaviour (82 per cent in non-M) ($P < 0{\cdot}05$). We did not find significant differences with respect to tumour stage, frequency of vascular invasion, tumour lymphocytic infiltration, and PCNA labelling index.

Conclusion: The current results provide data supporting the genetic and clinicopathological differences between mucinous and non-mucinous colorectal carcinomas. The consideration of both tumours as distinct entities with different pathways of carcinogenesis and different clinical features is recommended.

Photodynamic method used for treatment of primary and metastatic skin tumours

J. Domaniecki, E. Stanowski, A. Graczyk, W. Kozłowski, J. Struzyna, Z. Mierczyk, M. Kwaśny, M. Najdecki and J. Krupa Central Clinical Hospital, Military Medical Academy, Optoelectronics Institute, Military University of Technology, Warsaw, Poland

A photodynamic method is successfully applied for tumour diagnosis and treatment. We used such a method for a dozen or so patients with primary and metastatic skin tumours. As photosensitizers HpD (Arg)2 and PP(Ala)2(Arg)2 were used in concentration of 1 mg/ml. The photosensitizers were administered directly into tumours with a dose of $\sim$10 mg/kg.

As a result of tumour irradiation by means of the He-Cd laser, a tumour intensively luminates what makes it possible to determine accurately its size and shape Next, we applied a series of irradiation by means of He-Ne laser during the successive three days and patients received full dose of 150 J/cm^2 per tumour surface For extensive tumours such an irradiation series was repeated after 7 days. The patients were divided into three groups depending on tumour size The first group of patients with tumours of 0·5 cm diameter showed very good treatment results just after the first series of irradiation The second group of patients with tumours of 0·5–1·0 cm showed very good treatment results after two series of irradiation The third group of patients with tumours of diameter over 1·0 cm showed acceptable treatment results after two series of irradiation was determined as sufficient. The patients from the third group were operated on (tumour resection) after 7–10 days from the time of the completed irradiation. The photodynamic method can be used as a method for tumour diagnosis and skin tumour treatment as well as a supplementary method for surgical intervention.

DNA flow cytometry of gastric carcinoma: corrrelation with clinicopathological findings

F. Esteban, D.S. De Vega*, R. Garcia†, R. Rodriguez‡, J. Manzanares§, M. Duran*, R. Sanz* and S. Tamames*
**Hospital Universitario San Carlos, Madrid, †F. Jiminez Diaz, Madrid, ‡H.V. Salud, Toledo, §H.G. Segovia, Spain*

Background: DNA ploidy and S-phase fraction measured by flow cytometry were shown to correlate with several clinicopathological findings in some types of tumours.
Material and methods: DNA flow cytometry was performed in 78 curatively resected gastric carcinomas, using paraffin-embedded samples and the findings were correlated with various clinicopathological data of the patients
Results: Thirty-nine of the 78 samples (50 per cent) are represented on an aneuploid histogram There was a marginally significant correlation between nodal involvement and aneuploidy ($P = 0{\cdot}07$). There was a trend for ulcerated and differentiated tumours to have aneuploid DNA content Survival was poorer for aneuploid tumours with respect to diploid cases ($P = 0{\cdot}04$) S-phase fraction was obtained in 38 samples of diploid cases and six cases of normal gastric mucosa. The mean value was 16·1 ± 6·8 per cent for control cases and 21·1 ± 9·3 per cent for the tumours. Sixteen cases (41 per cent) show a high S-phase fraction (22 per cent). Higher S-phase of tumours was correlated with location and size ($P = 0{\cdot}01$).
Conclusions: The overall frequency of aneuploidy was 50 per cent in gastric carcinoma. DNA ploidy showed marginally significant correlation with nodal involvement Aneuploidy was associated with poorer prognosis. S-phase fraction showed significant correlation with tumour location and size.

Hyperthermic antiblastic perfusion with TNF-α and melphalan in the treatment of stage II–III limb melanoma

F. Di Filippo*, F. Cavaliere*, C.R Rossi†, M. Anzà, F. Cavaliere*, R. Garinei*, M Schiratti, A. Vecchiato†, M. Lise† and R Cavalieri* **First Department of Surgery, Regina Elena Cancer Institute, Rome, †First Surgical Clinic, University of Padoa, Italy*

Introduction: Excellent results with hyperthermic perfusion (40°C), melphalan and high-dose TNF (3–4 mg) for the treatment of stage II–III limb melanoma have recently been reported by Lienard, showing a complete tumour response rate of 90 per cent. The therapeutic index was partially lowered by TNF-correlated systemic toxicity consisting of cardiovascular and pulmonary failure in most of the patients treated. It has been shown that the melphalan and TNF tumoricidal effect is temperature-dependent Therefore, a temperature increase up to 41°C might result in at least an isoeffect with lower TNF doses Consequently, the systemic toxicity should be reduced, providing a higher therapeutic index.
Aim: A phase I study was therefore conducted with the aim of establishing the maximum tolerable TNF dose in association with true hyperthermia (≥41°C).
Materials and methods: Fifteen patients have been treated thus far (11 females, four males, age range 37–60 years, average age 48 years). Seven patients had stage IIIA disease, seven had stage IIIAB and one stage IV disease because of distant skin metastases. The number of lesions ranged between one and 23 with an average of six lesions Six patients had already been treated with regional perfusion, four with two regional perfusions Systemic toxicity was mild (maximum TNF dose. 3·3 mg) and only G3 pulmonary toxicity was recorded in one patient treated with a TNF dosage of 3·3 mg
Results: Regional toxicity consisted of mild and transient limb erythema and oedema in 14 patients (grade II) and a grade III limb reaction occurred in only one patient treated with a TNF dose of 3·3 mg. A CR was obtained in 10 out of the 15 patients (67 per cent), a PR was achieved in five (33 per cent) (in two, the PR was ≥90 per cent) and the OR was 100 per cent. Regional relapse occurred in three patients (20 per cent), 3, 6 and 14 months, respectively, after the treatment. Systemic relapse (pulmonary) was recorded in two patients, 12 and 13 months after the regional perfusion. Two patients died of disease, 15 and 25 months after treatment The other 13 are alive with NED at a median follow-up of 12 months.

Partially supported by C.N R. A.C R O. no 9501264PF39.

Development of MR-guided interstitial laser coagulation for solid tumours

J. Heisterkamp*, N.A.A. Matheijssen†, R van Hillegersberg*, J. Stoker†, J.J. van Vaals‡, J.S. Laméris† and J.N.M. IJzermans* *Departments of *Surgery and †Radiology, University Hospital Rotterdam and ‡Philips Medical Systems, Best, The Netherlands*

Interstitial laser coagulation (ILC) is a new minimally invasive technique that holds the promise of becoming a local treatment modality for solid tumours, such as hepatic metastases, pancreatic carcinoma and breast cancer. Several experimental studies have shown the feasibility of this approach, however clinical application is limited e.g because of lack of reliable on-line monitoring of the laser-induced effects.
Aim: We evaluated the feasibility of MR-phase temperature mapping as a method of on-line monitoring in ILC
Materials and methods: Experiments were performed in *ex vivo* porcine livers at room temperature. Nd·YAG laserlight ($\lambda = 1064$ nm) was guided through one ($n = 20$) or two ($n = 10$) cylindrical diffusing laser fibres. Laser output was 6 W per fibre for 6 min. After laser application the livers were dissected and the coagulated volume as assessed. Twenty experiments (10 single- and 10 dual-fibre) were performed with respiration simulation with the liver on a moving table (excursion 40 mm, frequency 12/min). Ten experiments (single fibre) were performed without movement. On-line MR temperature mapping was performed on a 1.5 Tesla system (Philips Gyroscan ACS-NT). Three orthogonal slices were acquired, angulated parallel and orthogonal to the laser fibres One scan was made, before laser application, to obtain a baseline image Dynamic scans were made during laser application to follow the temperature effect. The temperature images were displayed as multicolour overlay.
Results: The temperature increase was clearly visible on the MR scan during ILC. The subsequent temperature decrease, after laser application, could also be followed For analysis we used the images on which maximum temperature increase was displayed. The mean area without movement was 18 × 18 mm (single fibre), with respiration simulation 17 × 14 mm (single fibre) and 36 × 22 × 16 mm (dual fibre). Corresponding macroscopic visual coagulation sizes were 23 × 13 (single fibre) and 35 × 26 × 16 mm (dual fibre).
Conclusion: MR-phase mapping shows considerable promise as reliable on-line monitoring device to realise a successful minimally invasive approach in the treatment of liver metastases by ILC.

Analysis of 129 pelvic exenterations for gynaecological malignancies

G. Houvenaeghel, V Moutardier, F. Bladou, J. Hardwigsen, M. Martino and J.R. Delpéro *Institut Paoli-Calmettes, 232 Bd Sainte Marguerite, Marseille Cedex 9, France*

One hundred and twenty-nine patients underwent pelvic exenteration between January 1980 and December 1995 in the Department of Surgery of the Institut Paoli-Calmettes, [50 anterior, 35 total (29 supralevator exenterations), 32 posterior (20 supralevator exenterations), 12 atypic procedures] The mean age was 52·5 ± 11 9 (range 26·8) years.

Ninety-two exenterations were done for carcinoma of the cervix (71 per cent) Thirty-seven were done for other malignancies 13 endometrium, 11 ovarian carcinoma, four vagina, four sarcoma, two vulva, two fallopian tube, one mullero blastoma There were 52 primary exenterations and 77 secondary exenterations for recurrence The resection was considered retrospectively to be curative in 69 cases [31 primary exenterations (59 per cent) and 38 secondary exenterations (49 per cent)] and palliative in 60 cases [21 primary exenterations (41 per cent), and 39 secondary exenterations (51 per cent)] Forty-eight low colorectal anastomosis were performed among 67 posterior and total exenterations (73 per cent): in 20 of 32 posterior (62·5 per cent) and 28 of 35 total exenterations (83 per cent) Colorectal anastomosis was performed by hand suture in eight patients and by end to end stapling in 40 patients A protective transverse colostomy was fashioned in 32 patients A urinary derivation was made in 87 cases 15 bilateral cutaneous ureterostomy before 1984, 54 transintestinal ureterostomies, 18 (modified Indiana Pouch) performed by continent urinary diversion, 31 epiplooplasties and 14 vaginal pelvic feeling with reconstructions using rectus abdominal myocutaneous flap The hospital mortality was 10 per cent (13/129) The morbidity was 50 per cent (64/129). The overall actuarial survival was for all patients, 45 per cent, 30 per cent and 27 per cent at 2, 3 and 5 years, for the curative group (n = 69), 68 per cent, 60 per cent and 44 per cent at 2, 3 and 5 years, for the palliative group (n = 60), 16 per cent, 10 per cent and 5 per cent at 2, 3 and 5 years

Better results were observed in the group of primary exenteration considered as curative (n = 31) with a 2, 3 and 5 years actuarial survival of 76, 70 and 54 per cent, and in the group of pelvic exenteration for recurrence considered as curative (n = 32) with a 2, 3 and 5 years actuarial survival of 62, 50 and 36 per cent at 2, 3 and 5 years.

Primary retroperitoneal tumours

G. Ionescu, S. Jianu, S. Paun and B Gaspar *Department of Surgery, Emergency Hospital (Spitalul Clinic de Urgenta), Calea Floreasca nr. 8 sectorul 1 Bucharest, Romania*

Nineteen cases of primary retroperitoneal tumours treated in our hospital during 1992–1995 are retrospectively analysed

The predominant clinical picture consisted of abdominal pain and digestive symptoms (68 4 per cent, 13 cases) with palpable abdominal mass in 57 9 per cent of cases (11 patients) Patient information, clinical data and radiological findings (including computed axial tomography) established the correct diagnosis in 79 per cent of cases (15 patients) Histologically, mesodermal malignant tumours were predominant Surgical treatment was performed in all patients, seven patients underwent radical resection and six patients partial resection and biopsy was performed Operative mortality was 10 per cent (two patients). One-year and four-years survival rates were of 68 4 per cent (13 patients) and 36·8 per cent (7 patients), respectively

We concluded that successful treatment of primary retroperitoneal tumours is improved by rapid and correct preoperative diagnosis and radical resection

Strategy for thyroid carcinoma surgery: impact of frozen section analysis

J.L. Jansens*, Y. Sokolow*, N. Nagy†, K. Delbecque†, I. Salmon†, M. Cappello*, and P. Rocmans* **Departments of Thoracic Surgery and †Anatomopathology, Hospital Erasme, Université Libre de Bruxelles, 808, Route de Lennik 1070 Brussels, Belgium*

Thyroid carcinoma represents about 1 per cent of all malignancies, and is the most common endocrine cancer. Although thyroid carcinoma is generally considered a disease with good prognosis, it is important to have an accurate diagnosis for the initial treatment. The fine-needle aspiration cytology (FNAC) is the best way to get a preoperative diagnosis At surgery, frozen section analysis by an experienced pathologist, provides much more information about the most appropriate resection, related mainly to cell type and TNM. In this retrospective study, 132 thyroid cancers resected were reviewed between 1979 and 1996 Histological types were. 81 papillary, 15 follicular, 13 anaplastic, nine medullary, four Hurtle and 10 miscellaneous Preoperative FNAC was performed in 99 patients: 56 revealed cancer, 10 were suspected of cancer and all were confirmed on surgical specimen. Frozen section analysis was made in 126 patients and showed 98 (78 per cent) thyroid cancers. There was no false-positive and 28 false-negative diagnoses· 11 of these 28 were microcarcinoma and the 17 others were attributed to errors of sampling, technical artifacts related to frozen section or areas outside the main nodules. We conclude that frozen section analysis may be very useful for guiding the initial surgical therapy.

Detection of malignant melanoma of the skin using autofluorescence

W. Jędrzejczyk, B.W. Chwirot, S. Chwirot, J. Redziński, K. Telega and V. Poźniak *Interdisciplinary Group of Optical Methods of Early Detection of Cancer, Copernicus University, Toruń, Poland*

In this paper we present a new, non-invasive method of *in vivo* detecting melanoma malignum of the skin. We performed our studies on the basis of 150 pigmented lesions. Autofluorescence (AFL) of tissue depends on its native biochemical status With ultraviolet light from a high-pressure lamp, the AFL spectra of human melanoma malignum and surrounding healthy skin were excited and recorded Usually the intensity of AFL was very low within a melanoma malignum. We observed a local increase of AFL intensity within corresponding normal tissues Such a typical distribution of AFL intensity has never been found for benign naevi Thus it can be taken as a criterion for melanoma malignum diagnosis. In 92 per cent of cases, histological examination following the surgical excision of the naevi confirmed the diagnosis previously established on the basis of AFL

The main factors affecting the survival of gastric cancer in advanced stage: univariate and multivariate analysis of 63 cases

N.A. Kama, F M. Avsar, T. Coskun, I.H. Kulacoglu and M. Doganay *Ankara Numune Hospital, 4th Department of Surgery, Ankara, Turkey*

Introduction: The relation between the overall survival and prognostic factors on the patients operated for gastric carcinoma was examined.

Patients and methods: The age, sex, tumoural localizations, dimensions of the mass, histopathological type of the tumour and the degree of differentiation, the depth of invasion into the gastric wall (pT), lymphatic metastasis (pN), distant metastasis, tumoural invasion in the surgical margins, macroscopic type (Borrmann's classification), microscopic type (Lauren's classification), vascular invasion, neural invasion, and the peroperative blood transfusions were evaluated, taking into account the effect of these factors, using univariate and multivariate analyses in 63 out of 106 patients; operated with the diagnosis of gastric carcinoma between 1 January 1995 and 3 November 1995 in our department. Forty-two of the patients were males, 21 were females ($n = 63$), the mean average age being 56 years. The patients were followed between 1 to 36 months (average 12 months) Thirty patients died within 1–29 months postoperatively, on the other hand 13 patients have been living for 3–36 months (average 21·1 months) without complaints.

Results: The age, the diameter of the mass, the depth of transmural invasion (pT), histological type, the degree of differentiation and the vascular invasion were seen to affect the survival in univariate and multivariate analysis.

Conclusion: Of these factors the vascular invasion, histological type of tumour, differentiation and lymphatic metastasis were found to be the most significant parameters with respect to prognosis ($P = 0{\cdot}0070$, $P = 0{\cdot}0148$ and $P = 0{\cdot}0188$).

P-glycoprotein expression in frozen and paraffin gastric carcinoma tissues using a panel of monoclonal antibodies

F.J Lacueva, A Teruel, M.J. Mayol, J.A Ferragut, R. Calpena, J Medrano, J.A. Barreras and M.T. Pérez-Vazquez *Elche University General Hospital and the Departments of Pathology and Surgery, and Neurochemistry of Alicante University, Spain*

Anthracyclines are commonly used in adjuvant therapy for gastric cancer To evaluate the most sensitive method for detecting P-glycoprotein expression, we determined it in frozen and paraffin-embedded carcinoma tissues using a panel of antibodies. Fifteen gastric adenocarcinomas were evaluated for expression of P-glycoprotein in frozen and paraffin-embedded samples. For paraffin-embedded tissues the immunoperoxidase 'sandwich' staining method for amplified detection of P-glycoprotein described by Toth *et al* was used C219, JSB-1 and C494 antibodies were tested for both kinds of samples Additionally, MRK16 was tested in frozen samples. The Friedman test was used for statistical analysis All of the adenocarcinomas showed P-glycoprotein expression in different degrees when JSB-1 and C494 was used as the primary antibody in paraffin samples compared to 13 carcinomas (87 per cent) shown in frozen tissues with the same antibodies, although this difference was not significant. Ten (67 per cent) and seven (47 per cent) of the adenocarcinomas expressed P-glycoprotein by C219 in paraffin and frozen tissues and eight (53 per cent) of the frozen samples did when MRK16 was used When all of the antibodies were compared, JSB-1 and C494 were found to be more sensitive for detection of P-glycoprotein expression than C219 and MRK16 ($P < 0{\cdot}00001$). Our preliminary results show that P-glycoprotein expression has been underestimated in the past and that gastric adenocarcinomas usually express P-glycoprotein. We recommend the use of JSB-1 and C494 as primary antibodies and the immunoperixodase 'sandwich' staining method for amplified detection of P-glycoprotein for paraffin-embedded samples to evaluate P-glycoprotein expression in gastric adenocarcinoma.

The completion thyroidectomy in the treatment of differentiated thyroid carcinoma

A Malloci*, A. Nicolosi*, P G. Calò*, C. Meleddu†, B. Massidda*, M L. Carcangiu* and A. Tarquini* *Università di Cagliari, *Istituto di Chirurgia ed Oncologia, †Ospedale Oncologico, Servicio di Medicina Nucleare, Via Jenner, Cagliari, Italy*

The purpose of the study is to review complications and survival rates in 60 patients treated with completion thyroidectomy (CT) plus ^{131}I for differentiated thyroid carcinoma (DTC).

In our Institute, from 1973 to 1995, 60 patients (10 males, 50 females, median age 37 years, range 18–74 years) were operated of CT, from 2 to 36 days after partial thyroid resection. There was no operative mortality. In four patients temporary recurrent nerve palsy and in two patients permanent hypoparathyroidism occurred Of cancers, 44/60 (73 per cent) were papillary, 15 (25 per cent) follicular, 1/60 was a Hurthle carcinoma; 21/60 (35 per cent) of cancers were bilateral. Of 60 patients, 13 (three males and 10 females) were at high risk of recurrence of disease After an average follow-up of 100 months (range 5–276 months), one patient is dead (after 102 months). Three patients had a recurrence, treated with ^{131}I two of them are DF Survival rate is 98 per cent at 10 years (by actuarial method), with no difference with survival rate of normal population

Our results support our opinion that CT is a safe surgical procedure It is indicated in all patients with high-risk DTC In our opinion, it is indicated also in all low-risk patients, because it gives more chances of curing the disease it eradicates bilateral cancers (very difficult to discover), it permits ^{131}I radiotherapy and a more sensitive follow-up We need more information on outcome after 20 or more years of follow-up to support the opinion that conservative surgery of DCT is more curative than total thyroidectomy plus ^{131}I-RT.

Sulindac as a non-steroid anti-inflammatory substance: does it have an effect on partly proliferating, partly neoplastic mucosal lesions within a precancerous situation in the rat stomach?

S. Maurer*, G. Winde*, P. Dinse*, B. Marschall*, K.W. Schmidt† and B. Sprakel* **Department of Surgery and †Gerhard-Domagk-Institute of Pathology, University of Münster, Jungeblodtplatz 1, 48129 Munster, Germany*

Sulindac (2 mg) per day were administered in 20 Wistar rats for a period of 3 months. Prior to the Sulindac treatment all animals had been given nitrosamines in the drinking water for a period of 2 years. Fourteen animals underwent stomach resection in addition to the administration of nitrosamine. The intention of our study was to investigate the effect of both nitrosamine and Sulindac on the development of premalignant and malignant mucosal lesions.

To examine the effect of Sulindac on the proliferative and invasive behaviour of the stomach epithelium, biopsies were taken before and after the administration of Sulindac. They were examined morphologically as well as immunohistologically using the E 9 antibody to metallothioneine (MT). Morphologically, the changes shown in Table 1 were observed

Findings before Sulindac application	Findings after Sulindac application
Intact mucosa 16	Intact mucosa 11
Adenomatous-cystic proliferation (ACP) 2	Adenomatous-cystic proliferation 6
Early carcinoma 2	Early carcinoma 1
Advanced carcinoma 0	Advanced carcinoma 2

Table 1 presents that before administration of Sulindac four animals had a pathological mucosa whereas after administration of Sulindac nine animals showed premalignant or malignant lesions MT-negativity was observed in intact mucosa, ACP and advanced carcinomas. All early carcinomas showed MT-overexpression. This study fails to prove an inhibitory effect of Sulindac on the proliferative and invasive behaviour of the stomach epithelium within a precancerous condition in the rat stomach. The overexpression of MT which was only found in early carcinomas may indicate cellular stress reaction of the stomach epithelium under strong proliferative pressure.

The surgical treatment of suprarenal metastases caused by bronchogenic carcinoma: our experiences

U. Pandolfi*, M. Benedetti*, R. Marchesi*, A Zanardi*, D. Scicchitano*, V Ronchi*, A. Pastorelli* and S. Rizzo†* **Policlinico 'S. Matteo', Surgery Department, General Surgery Section B, †Pneumology Division, The University of Pavia IRCCS, Pavia, Italy*

Suprarenal metastases are frequently present in the most advanced phases of lung tumour (4th stage), and so it is rarely confronted surgically

In our surgical division during the years 1989–95 we surgically treated 147 cases of pulmonary neoplasia. The presence of a single suprarenal metastasis in absence of other localizations of the disease was revealed in four cases (2·7 per cent) The patients were all male and between the ages of 61 and 72 years. We subjected these patients to suprarenelectomy In two cases where the metastasis was localized homolaterally to the primary tumour and due to good general preoperative conditions, we opted for a simultaneous treatment with a thoraco-phrenotomic approach; while in the remaining two cases, where the general conditions of the patients were not very good, the suprarenal metastasis was confronted subsequently The operations on primary neoplasia were three left superior lobectomies and a left pneumectomy Patient follow-up allowed for the observation of survival, which in two cases was less than 6 months (2–6 months) and in the other two cases was more than 2 years (living between 24 and 27 months) The analysis of these data, even if not of statistical significance due to the small sample, and in comparison to other literature, allows us to affirm that synchronous or deferred surgical treatment of a single suprarenal metastasis can in some cases lead to an increase in the length of survival

A pilot study of adjuvant hepatic arterial infusion chemotherapy, associating 5-fluorouracil and leucovorin, after resection of colorectal cancer liver metastases

H. Porte, H. De Moulins, L. Gambiez, P. Puech, A Wurtz and P. Quandalle *Hospital Calmette, Clinique Chirurgicale, Boulevard du Pr Leclercq, 59037 Lille Cedex, France*

The impact on survival rate of adjuvant chemotherapy after resection of colorectal liver metastasis is not clearly defined. In this context, we initiated a pilot study of adjuvant hepatic arterial infusion chemotherapy (AHAIC) associating 5-Fluorouracil (5-FU) and leucovorin to assess: (a) the feasability, (b) the side-effects, (c) the eventual effects on the patterns of recurrence of this protocol. Hepatic arterial infusion ports were placed in 15 consecutive patients undergoing potentially curative resection of colorectal liver metastasis. Primary colorectal tumour had been resected without any evidence of local recurrence or extra hepatic metastatic disease. The protocol started between day 10 and 15 after liver resection. The chemotherapy regimen consisted of a weekly infusion of 5-FU (12 mg/m^2/per day) and leucovorin (200 mg/m^2/per day) for 12 months. The mean follow-up was 28 months (range 10–72 months) There was no clinical or biological complication related to chemotherapy except for sharp epigastric burns in four patients immediately after five FU infusions. Catheter irreversible occlusions led to early cessation of the treatment in three patients. Early cessation of the protocol was necessary in two other patients justified by extrahepatic colorectal recurrences discovered 2 and 7 months after liver resection, respectively. Four of the 15 evaluable patients developed recurrent disease The site of relapse was liver in two patients and extrahepatic sites in the two remaining patients. Three of these four patients died of their recurrent disease 9, 26 and 33 months after liver resection, respectively. The remaining 11 patients (73 per cent) are alive without any evidence of disease at 10, 10, 10, 12, 13, 21, 22, 36, 56, 58 and 72 months after liver resection.

Conclusions: 5-FU and leucovorin can be combined for AHAIC in a long duration regimen with a very low extent of side-effects This protocol could be safely employed in a prospective randomized study in combination with 5-FU systemic infusions in order to prevent both intra- and extrahepatic recurrences.

Von Recklinghausen disease: neurofibrosarcoma, malignant degeneration: case report

R.J. Sala, A. Sánchez Marín, J.J. Sánchez Cano, F. Guspí, E Just, R. Pla and D. Del Castillo *Hospital Sant Joan Reus, Universitat Rovira i Virgili, C/ Sant Joan s/n, Reus, Tarragona, Spain*

Introduction: Neurofibrosarcomas (NFSs) are rare tumours that comprise approximately 5–10 per cent of all soft-tissue sarcomas. These tumours can occur spontaneously after radiation, after malignant degeneration of a solitary neurofibroma, or in conjunction with Von Recklinghausen's disease (VRD). This tumour has been known by several other names, including malignant schwannoma, malignant neurilemmoma and neurogenic sarcoma. We present a clinical case of a patient and objectify the development of an NFS upon the base of a VRD, and that gave us the reason to do an update of this disease

Case report: We present a young female, 32 years old, with mental deficiency and diagnosis of VRD from puberty, disease that develops a malignant course from 10 years ago Showing up successively NFS on left internal sciatic popliteous nerve, left median nerve and right vagus nerve. In the last location was identified histologically a malignant schwannoma of third grade, with an ominous progression in spite of the surgery, radiotherapy and chemotherapy.

Discussion and conclusions: The clinical presentation of NFS is similar to that of other soft-tissue sarcomas. The majority of NFSs are found in patients who carry a diagnosis of VRD The study by image techniques contribute in the surgical strategy marking the limits of the tumoural mass. The rapidly enlarging mass in a patient with VRD must lead us to suspect malignancy, and consequently we must do a biopsy of the mass, the definitive diagnosis being histological. The treatment will be based on a wide and radical surgical resection, less aggressive measures have had a high local recurrence rate Unfortunately, the radiation therapy and chemotheray are often unsuccessful, although they can aid in local and systemic control respectively.

Despite this aggressive treatment, prognosis remains guarded in most cases, with a 5-year survival rate of 23 per cent in patients with VRD.

Malignant melanoma of the cervix uteri: a case report and review of the literature

E Salle, G Houvenaeghel, F. Bladou, J. Jacquemier, K. Antoine, J. Hardwigsen, R. Legre and J R. Delpéro
Institut Paoli-Calmettes, 232 Bd Sainte Marguerite, 13273 Marseille Cedex 9, France

A case of primary malignant melanoma (MM) of the cervix uteri is reported. A vaginal hysterectomy was performed on a 39-year-old woman presenting with metrorrhagia and cervical dysplasia Immunohistochemistry studies of a macroscopic pigmented nodule with induration and infiltration was in favour of MM A junctional activity of the MM within the cervix mucosa asserted the primarity of the disease After laparotomy, the surgical margins were positive for the parametrium and the vagina. In our institute, clinical and endosonography showed involvement of right lateral and posterior walls of the two proximal third of the vagina Total vaginectomy was performed, with vaginal reconstruction using a rectus abdominis myocutaneous flap An additional treatment with Interleukin 2 was given. The patient committed suicide 44 months after surgery and was considered NED It is an exceptional (35 cases described), highly malignant disease, with a 5-year survival rate lower than 5 per cent. The death occurs between 6 months and 4 years after diagnosis, and only two cases of long-term survival (more than 10 years) have been described Disease at diagnosis is generally advanced because of a silent tumour development, and a difficult diagnosis on cervical smear examination. Thus, the diagnosis is mainly based on immunocytochemistry studies (Vimentin, S-100, HMB45) on surgical specimen or biopsy The general staging is similar to the one used for cervix uteri epithelioma After careful skin examination to eliminate a primitive skin MM, junctional activity of MM within the cervix mucosa is enough to assert the primarity of the disease. The only curable treatment is an en-bloc resection of vagina, uterus, parametrium, and pelvic lymph nodes. When performed, the vaginal reconstruction uses preferentially a rectus abdominis flap, but this reconstruction is debated Pelvic radiation therapy is not appropriate in this indication. Chemotherapy should be used in clinical trials in case of metastatic disease However, immunotherapy is a promising and well tolerated therapy in these rare cases.

Immunotherapy with rat colon carcinoma cells in liver metastasis model

F. Stipa*, I. Sirovich*, S. Cesareo*, F. Tagliaferri*, A. Zolovkins†, A. Lombardi*, M.G. Valente*, A.V Sterpetti* and A. Cucina* *Ist Department of Surgery, University 'La Sapienza', Rome, Italy, †Department of Surgery, Riga 7th Hospital, Medical Academy, Latvia

The immunotherapeutic approach for the adjuvant treatment of colon adenocarcinoma is currently under evaluation

The aim of this study was to assess the effect of vaccination with autologous tumoural cells, modified by Newcastle virus, in rats with hepatic metastasis, inducted by cellular line of colon adenocarcinoma. Thirty 4-week-old male BD IX rats were injected through mesenteric vein with 10^6 cells autologous cells, obtained from colon adenocarcinoma line DH12KD. Diffuse hepatic metastasis developed in all rats of the control group (20 rats) The treated rats were divided in two groups, according to the different modalities of administration The vaccine was obtained from tumoural cells line DH12KD and injected subcutaneously In the first group (10 rats) vaccination was performed once a week starting 3 weeks before tumoural induction and weekly for 7 more weeks In the second group (10 rats) the first vaccination was performed at the same time with the induction of the tumour and another one 7 days later

The log-rank test to compare the Kaplan–Meier survival curves showed longer survival for the rats of the first group ($P = 0{\cdot}01$), and similar survival in rats of the control and the second groups ($P = 0{\cdot}7$)

This experimental model is valid to study the effect of immunotherapy as adjuvant treatment of colon adenocarcinoma. This study shows also that active specific immunotherapy is more effective when vaccination is started before tumour induction and is prolonged for a long time.

Influence of the bFGE on growth of mammary carcinoma in an experimental model

F. Tagliaferri*, F. Stipa*, S. Cesareo*, I. Sirovich*, M.G. Valente*, A Zolovkins†, A. Lombardi*, A. Di Carlo*, A. Cucina* and A.V. Sterpetti* *Ist Department of Surgery, University 'La Sapienza', Rome, Italy, †Department of Surgery, Riga 7th Hospital, Medical Academy, Latvia

Basic fibroblastic growth factor (bFGF) is an autocrine factor released by different tumoural cell lines probably involved in the neoplastic invasion process due to its angiogenetic property. The aim of this study was to evaluate different growth characteristics of four clones of rat mammary carcinoma and their relation with bFGF release

The four different clones were obtained from the cloning of primary culture of a hormone responsive ductal mammary carcinoma induced by intragastric 7–12 dimethylbenzanthracene (DMBA) injection in female Sprague–Dawley rats The different clones have been subsequently characterized for morphology, DNA and protein content (by cytofluorimetry) and structural cytoskeleton protein content. In order to investigate the growth characteristics, each clone was tested with tritiated thymidine growth assay. To evaluate the production of growth factors, supernatant of serum free cultures were tested on 3T3 Swiss by 3H-thymidine. Presence of bFGF was tested by an immunoenzymatic ELISA assay with a mouse\polyclonal antibody against bFGF. There is a difference between growth characteristics and releasing of bFGF as was proven by 3H-thymidine assay and evaluated by immunoenzymatic ELISA test. (Table 1).

These data demonstrate the development of different cellular clones from the same tumour with differences in growth characteristics and bFGF release rate. This *in vitro* model does not show correlation between bFGF and cellular growth.

Cellular clones	A	B	C	D
bFGF (ng/10^6 cells)	22 ± 4	85 ± 9	29 ± 5	38 ± 6

Pelvic recurrence after rectal cancer surgery: risk factors and treatment

M. Tedesco, M. Cosimelli, F. Ambesi Impiombato, D. Giannarelli, C. Botti, R. Mancini and R. Cavaliere *Regina Elena Cancer Institute, V. le Regina Elena 291, 00161 Rome, Italy*

Aim: The present study has been aimed to analyse both the risk factors for pelvic recurrence after radical surgery for primary rectal cancer and results from different therapeutic procedures in recurring patients.

Materials and methods: A total of 206 consecutive patients with primary rectal cancer submitted to radical surgery between 1980 and 1995 were included. The Multivariate Regression Analysis using the Cox Proportional Hazards model (MRA) identified the factors affecting pelvic recurrences An overall series of 44 patients were treated for pelvic recurrences, 12 patients were treated with surgery ± pelvic radiotherapy (XRT) ± chemotherapy (CH), 11 with XRT alone, nine with surgery alone, eight with CH ± XRT while four patients were not treated. The median follow-up was 44 months (range 1–62 months), 19 of them underwent surgery for the primary at other hospitals.

Results: Three variables have resulted statistically in terms of local recurrence-free survival (LRFS): (a) Dukes stage, $P = 0{\cdot}004$, (b) adjuvant XRT, $P = 0{\cdot}02$ and (c) the total mesorectal excision (TME) $P = 0{\cdot}01$. In only Dukes B patients the MRA showed XRT and TME as prognostic independent variables for 5-year LRFS ($P = 0{\cdot}0002$ and $P = 0{\cdot}04$, respectively).

With regard to results of treatment of the 44 pelvic recurrences, the actuarial overall 5-year survival was 14·9 per cent. Surgery ± XRT ± CH provided the highest 5-year survival rates (41·7 per cent *vs* 0 per cent in the remaining subgroups of treatment, $P = 0{\cdot}005$) Particularly, the surgery alone subgroup showed a 5-year survival similar to that submitted to surgery and XRT ± CH (43·7 per cent *vs* 39·8 per cent, P = n s.) However, the 5-year disease-free survival after surgery ± XRT ± CH was 12 per cent.

Conclusion: The combination of surgery and XRT is crucial for both minimizing the risk of pelvic recurrence and providing the highest chances of local control and survival Surgery alone is to all appearances the most effective treatment because of the most favourable selection of patients with only anastomotic recurrence.

Partially supported by Project A I R C n° 95/30/R/42 and Project C.N.R. A.C.R.O. n° 9500482PF39

Recurrent colorectal carcinoma treated by IORT through afterloading-flap technique

C. Tonus, C. Kolotas, P. Appel and H. Nier *Stadtische Kliniken Offenbach, Chirurgische Klinik I, Starkenburgring 66, 63069 Offenbach, Germany*

Intraoperative radiotherapy is a new concept in the treatment of noncurative resectable recurrent colorectal tumours. With the afterloading-flap technique an increased local radiation dose combined with lowest strain of surrounding viscera, aiming at lower recurrence rate, is possible

Between October 1995 and April 1996, 15 patients with advanced, R1 or R2 resected colorectal tumour recurrence received IORT. Chemo- and percutaneous radiotherpay had already been applied to all patients The intraoperative irradiation was performed through HDR-Iridium afterloading A flexible flap, individually adapted to the tumour bed, was used for appliance. The applied contact dose was 10 Gy

The mean operation time (one hemicolectomy, six rectal resections, eight debulking) increased 30 min at average. The postoperative course was free of complications. Without additional therapy the patients were tumour-recurrence free for 12 months at average

Carcinoma of pancreas: surgical treatment

Z. Wajda, Z. Gruca, Z. Sledziński, T. Wysocki, J. Reszetow and Ł Kaska *II Department of Surgery, Medical University of Gdańsk, 1, Prof. Kieturakis St, 80-742 Gdańsk, Poland*

Between 1972–1994, 205 patients with pancreatic cancer were treated in our department The radical operation rate achieved 18 per cent· 37 curative procedures were performed. The perioperative mortality rate due to radical treatment was revealed to be 13 5 per cent. Late results of surgical treatment of pancreatic cancer were as follows· laparotomy median survival time 2·5 months; palliative procedures 6 months; but after radical treatment survival was significantly better, more than 17 months Results of surgical treatment of pancreatic cancer are still unsatisfactory mainly due to the advanced stage which excludes radical procedures.

Totally implantable venous access catheter devices for the administration of chemotherapy and other i.v. medication

R. Wilhelm and F. Massarani *Centre Hospitalier de Luxembourg, 4, rue Barblé, L-1210 Luxembourg*

From 1989 to 1995, 286 totally implantable venous access catheters (Implantofix) were inserted in 230 patients. The advantage of this device with the large base of its reservoir and the small diameter of its tubing is described. The technique of its implantation is explained. Follow-up was done on all patients until their death or up to this date. Indications were chemotherapy for neoplastic diseases (especially breast cancer and lymphoma), i.v administration of special medications in HIV patients, transfusions and hyperalimentation Complications although few, consisted in catheter injection, thrombosis of the tubing, leakage and haematoma The uses of the Implantofix catheter is convenient to both patients and nursing personnel.

Lymphangiomas in children

I P. Zhurilo, V.K. Litovka, V P. Kononuchenko and A.V. Scherbinin *Department of Child Surgery, Donetsk Medical University, Ilyicha avenue, 16, Donetsk, 340003, Ukraine*

Lymphangioma is one of the most frequent non-malignant tumour in children (9–18 per cent of all) This disontogenetic tumour has infiltrative growth and can often be complicated with inflammation

We observed 324 children at the age of from 1 month to 14 years for the last 10-year period. 180 subjects (55·6 per cent) were boys and 144 (44·4 per cent) were girls. External localizations of lymphangiomas were discovered in 297 patients (91·7 per cent) and internal localizations in 27 (8·3 per cent) The diagnostic of external lymphangiomas was not difficult. Nineteen children have simple form of lymphangioma, 112 cavernous form, 140 cystic form, 26 children have mixed form (lymph haemangiomas).

The most frequent location of lymphangioma was at neck, proximal parts of extremities and axillary regions. The inflammatory symptoms took place in 33 cases Patients with internal lymphangiomas (25 patients) were hospitalized urgently (acute abdomen, intestinal obstruction, tumour of peritoneal cavity) Sonography, laparoscopy, computer tomography were used to confirm the diagnosis in addition to clinical symptoms. The most frequent localization was: small intestine mesentery in 11 children, retroperitoneal cavity in six, great omentum in five, liver in four and mediastinum in one

Radical operations were performed in 297 children with external lymphangiomas and in 24 patients with 'internal localizations of the tumours. Recurrence level was 3·7 per cent. There were three fatal outcomes Our clinical investigations have demonstrated the lymphangiomas structure and efficiency of radical operations

Staging and grading in 223 cases of colon adenocarcinoma

G.C. Zografos, E. Kontes, A Betsou and G. Androulakis *4th Surgical Clinic, Athens University, Greece*

Staging and grading in colon cancer is fundamental to the prognosis and the completion of the therapy. The aim of this study is to investigate the correlation between staging and grading in 223 cases of colon adenocarcinomas. The material of the study is 223 cases (118 males, 105 females), median age of 59 (range 24–91) years, operated-on in the period 1989–1994 with a histologically proven colon carcinoma.

The disease was staged according to Astler–Coller classification system and graded as well (G1), moderate (G2), or poorly (G3) differentiated tumours. According to our results in stage A ($n = 8$, 3·6 per cent) the correspondence differentiation is G1 0 per cent, G2 75 per cent, G3 25 per cent. In stage B1 ($n = 35$, 15·7 per cent) there were G1 11 4 per cent, G2 80 per cent, G3 8·6 per cent. In stage B2 ($n = 81$, 36·3 per cent) there were G1 7·4 per cent, G2 77·8 per cent, G3 14·8 per cent. In stage C1 ($n = 15$, 6·7 per cent) there were G1 0 per cent, G2 100 per cent, G3 0 per cent In stage C2 ($n = 84$, 37·7 per cent) there were G1 5·9 per cent, G2 61·9 per cent, G3 32·1 per cent. Seventy-three cases had a metastatic disease in the liver: A 0 per cent, B1 2·7 per cent (2), G2 100 per cent, B2 24·7 per cent (18), G1 5·5 per cent, G2 66·7 per cent, G3 27·8 per cent, C1 0 per cent, C2 72 6 per cent (53), G1 5·7 per cent, G2 54 7 per cent, G3 58 5 per cent.

In conclusion, patients with colon adenocarcinomas and metastatic disease had moderated and poorly differentiated type of neoplasm (G2 58·9 per cent, G3 35·6 per cent $P=0·001$)

Orthopaedics

Analysis of congenital hand deformities: a series of 650 patients with 925 affected hands

B. Cambier*, G. Matton*, L. De Smet† and S. Monstrey*
**Department of Plastic Surgery, University Hospital, Gent,*
†Department of Orthopaedic Surgery, University Hospital Pellenberg, Belgium

After comparing the Swanson and Dobyns classifications, preference was given to the Swanson classification as published in the 1991 GEM Monograph

In a retrospective study of 925 hand deformities in 650 patients (male $n = 330$, female $n = 320$) we analysed the validity of the proposed classification In 41 per cent of the patients we found bilateral and in 59 per cent unilateral involvement affecting the right and left sides about equally. Classification was easy in 796 hands (86 per cent), difficult in 61 (6·5 per cent) and impossible in 68 (7·5 per cent) hands. In 86 hands two deformities were present and 35 hands showed three deformities, yielding a total of 1081 anomalies Some patients presented different anomalies on different extremities. Failure of differentiation occurred most frequently (513), followed by failure of formation (184), duplication (143), undergrowth (77), constriction bands (60), generalized skeletal abnormalities (29) and overgrowth (7). Difficulties in classifying a deformity can be due to clinical doubt (transverse arrest and congenital amputations due to constriction bands) or to insufficient knowledge of the pathogenesis (transverse arrest, atypical cleft hand and brachysyndactyly) Although the Swanson classification is a workable instrument, some additions could reduce drastically the number of unclassifiable cases. We suggest the following additions: deformities limited to the thumb under radial ray deficiency, congenital trigger finger under failure of differentiation, Kirner's deformity under failure of differentiation.

Treatment of chronic osteomyelitis by resection of focus with bone fragment elongation

J. Krajničák *Department of Surgery, Hospital and Policlinic Lúčna 57, 040 15, Košice-Šaca, Slovak Republic*

Post-traumatic osteomyelitis is a serious treatment problem as there are various methods with differences in successful treatment completion

One of the successful methods is resection of osteomyelitis focus of a long bone with a subsequent elongation of bone fragments This way of treatment proved to be effective especially when the osteomyelitic foci are located in diaphysis and metaphysis of long bones Focus is always resected into a healthy bone issue If a defect is in diaphysis after resection, it is effective to perform osteotomy in both major fragments and prolong both of them It follows that substitution of a defect is speeded up. Providing that the focus is located near epiphysis, only the major central fragment of a long bone is elongated and replacement of a defect is slower. The elongation never exceeds 1 mm/day (0·5 mm twice a day). In case of greater elongation there is a danger of cyst formation in bone regenerate accompanied with all the negative consequences

Five patients with osteomyelitic focus in tibia were treated In three patients the focus occurred in diaphysis and the defect after resection ranged from 5 to 7 cm. In two of them the defect was in a lower third of the tibia and was 3 and 5 cm long after resection. The treatment was completed in 6 to 8 months. The Ilizarov fixator was used three times and Poldi-4 fixator twice.

The biggest advantage of this method is the replacement of a bone defect with its own newly formed bone (regenerated bone) without potential necrotic foci which are common when substitution is performed by either autotransplanted bone or homotransplanted bone. This method is definitely able to treat chronic post-traumatic osteomyelitis.

Pancreas

Pylorus preserving duodenopancreatectomy with pancreaticogastroanastomosis

P. Andronescu, A. Miron, C Andronescu and S. Bacaliuc *'N. Gh. Lupu' Hospital, Sos. Stefan cel Mare nr. 19–21, Bucharest, Romania*

After pancreaticoduodenal resection, a pancreatic fistula is observed in 10 per cent of cases with a mortality rate of 20–30 per cent. Restoring pancreaticoenteral continuity by a pancreatogastrostomy may be an adequate alternative and represents the aim of the present study From 1990 to 1995, 13 patients have undergone pylorus preserving duodenopancreatectomy with pancreatogastrostomy. Three modalities were used. direct posterior pancreatogastrostomy in seven cases, posterior Wirsungo-mucosal anastomosis in two cases with dilated pancreatic duct, and transgastric posterior pancreatogastrostomy in four cases, in which proper mobilization of the remaining pancreas was available The mortality rate was nil The morbidity rate was 8 patients (one pancreatic fistula with reintervention and drainage). Four patients needed postoperative insulin therapy for high levels of serum glucose Endoscopic examination with injections of pancreatic duct was performed in eight patients and good observation of the anastomosis was obtained in five.

These results confirm that pancreatogastrostomy is a safe procedure of pancreatic drainage whenever feasible.

Ductal decompression for the surgical treatment of chronic pancreatitis

P. Árkosy, I. Kovács, G Tamás and P. Sápy *2nd Department of Surgery, Medical University of Debrecen, Hungary*

The objective of this study was to compare the results of pancreatico-gastrostomy to pancreatico-jejunostomy in the surgical treatment of chronic pancreatitis. Between 1 January 1991 and 31 December 1995, 87 patients underwent ductal decompression because of chronic pancreatitis. At the 2nd Department of Surgery, Medical University of Debrecen, in the last 5 years, 39 pancreatico-gastrostomy, 30 pancreatico-jejunostomy, 12 cysto-pancreatico-gastrostomy and six cysto-pancreatico-jejunostomy have been performed

Pancreatic ducts abnormalities were diagnosed preoperatively by ERCP. The incidence of complications was about 10 per cent The most common complication was the bleeding in the early postoperative period. Considering late results, 74 per cent of the patients belong to the 'good result' group after ductal decompression. The authors suggest that in the case of correctly chosen indication for operation the drainage to both direction could be applied successfully in the surgical treatment of chronic pancreatitis

Radicality in pancreatic cancer resection

G. Balzano*, A. Zerbi*, B.E. Leone† and V. Di Caro*
*Departments of *Surgery and †Pathology, S. Raffaele Hospital, University of Milan, Italy*

Aim: To evaluate the incidence and the effect on survival of local residual tumour after pancreatic cancer resection.
Patients and methods: From 1986 to 1995, 119 consecutive patients underwent resection for pancreatic cancer Only ductal pancreatic adenocarcinomas were included. Surgical procedures were 103 pancreatoduodenectomies, 12 distal pancreatectomies, four total pancreatectomies Sixty-two patients received intraoperative radiotherapy (IORT) (range 15–25 Gy) in association to the resection. Operative mortality was 3 3 per cent (four patients) morbidity was 34·4 per cent (41 patients). Tumour stage and grading were considered for the survival analysis Survival curves were calculated by the Kaplan–Meier method, univariate analysis was performed by the log-rank test; the Cox method was used for multivariate analysis
Results: Forty-eight patients (40·3 per cent) had a tumour involvement of the surgical margins (R1 group) whereas 71 patients underwent a radical resection (R0 group) Of the R1 group, 30 patients had a macroscopic residual tumour on the peripancreatic vessels whereas the remaining 18 patients had only a microscopic tumour involvement of the resection margins The most frequently involved margin was the posterior one (35 patients); other positive margins included· pancreatic section line. 11 cases, anterior margin two cases, superior margin one case, bile duct one case, distal duodenum one case. The macroscopic tumour residue was more frequently described on the superior mesenteric and/or portal veins (25 cases) IORT was performed in 26 patients of the R1 group (11 patients with microscopic residue and 15 patients with macroscopic one) Median postoperative survival of R0 patients was 15 months *vs* 13 months of R1 group (log-rank $P < 0{\cdot}05$; box. $P < 0{\cdot}05$). In the R0 group, the actual 3-year and 5-year survival rates were 17 4 per cent (eight patients) and 11·8 per cent (four patients), in the R1 group they were 3·5 per cent (one patient) and 0 per cent, respectively. The survival was greater in the group with a microscopic involvement of the margins than in the group with a macroscopic residue (median postoperative survival 14 months *vs* 9 months, $P < 0{\cdot}05$) In the R1 patients who underwent IORT, median postoperative survival was 14 months, whereas it was 12 months for R1 patients without IORT (P = not significant)
Conclusion: Survival after pancreatic cancer resection is discouraging, even in patients with an apparently radical operation The operative radicality is necessary, but it is not enough to obtain long-term survival IORT can play a role in the neutralization of the microscopic tumour residue, but it does not seem effective in improving survival when the residue is macroscepic In these cases a more aggressive surgical policy, including vascular resection, therefore seems advisable.

Advantage of Wirsung drainage in Child operation

J. Baulieux, M Adham, J. Dubois, E. de la Roche, C. Ducerf and M. Pouyet *Department of Surgery and Organ Transplantation, Hospital de la Croix Rousse, Lyon, France*

From 1982 to 1994, 33 patients received a Child operation with temporary external drainage of the Wirsung-jejunal anastomosis. Indication for a Child operation were chronic pancreatitis (n = 8), pancreatic tumour (n = 14), duodenal tumour (n = 8), common bile duct carcinoma (n = 2) and lymphoma (n = 1). In these cases a Wirsung-jejunal anastomosis was associated to a drainage with a multiperforated catheter The catheter was passed proximally through the jejunum at 20 cm from the site of the anastomosis and exteriorized, through the abdominal wall The drain was removed at post-operative day 12 The pancreatic tissue at the site of the anastomosis was normal in 15 cases, the other had chronic pancreatitis lesions. The diameter of the Wirsung was $\leq$ 5 mm in 26 cases (range 2–7 mm) One patient had an anastomotic fistula and one had late anastomotic stenosis. There was no pancreatitis nor haemorrhagic complication of the pancreas. Many procedures aimed to secure the pancreatic anastomosis after the Child operation None of them can expect to abolish completely such a complication and some had their own complications

This method of Wirsung drainage is original and easy to perform It significantly reduces the rate of anastomotic fistula and does not cause any morbidity

Pancreatic cancer: a community hospital's experience

V. Boni, F Agresta, S. Pintaldi, G. Trentin, G. Colucci and G. Tonietto *Divisione di Chirurgia Generale dell'Ospedale Civile di Vittorio Veneto, Via Forlanini, 31029 Vittorio Veneto, Italy*

We report on our experience concerning staging and planning of therapy for pancreatic cancer From 1979 to 1995, out of 79 surgical procedures for pancreatic and periampullary region neoplasms done in our Department, 20 were performed with radical intent In 15 patients the histological diagnosis was positive for ductal adenocarcinoma (in the remaining five it was positive for periampullary carcinoma or insular carcinoma). seven patients were classified as stage III and the others as stage II according to the Hemreck classification. A total pancreatectomy was performed in five patients and a pylorus-preserving pancreatoduodenectomy in 10 (because we believe that this procedure avoids postgastrectomy symptoms and it does not compromise the radical intent and therefore the long-term survival of patients). The postoperative mortality was 13 per cent (one patient died from a pancreatic fistula due to neoplastic involvement of the remaining pancreas and the other died from pulmonary embolism). The median long-term survival is 14 months for patients in stage III (range 1–78 months) and 36 months for stage II patients (range 1–132 months) We have registered, in all patients, a good postoperative quality of life Today the choice of treatment for pancreatic cancer should be based on the possibilities afforded by the location and stage of tumour. For this reason, surgical resection is the choice of treatment for patients with no nodal metastasis (stage II) But microscopic involvement is fairly common in pancreatic cancer (stage III), even with small tumours (and normally it is diagnosed after surgery[1]) and should not be a contraindication to resection in selected patients. Also if the morbidity and mortality associated with pancreatic resection is still relatively high, it is the widely held view that pancreatoduodenectomy probably provides the best palliation for pancreatic cancer (with an acceptable long-term survival in some instances and good postoperative quality of life), so we also think that resection for intended cure is justified if it can be done without leaving gross residual cancer We want also to point out that the main goal for pancreatic cancer is its preoperative staging For this reason, as already reported in the literature, we are evaluating laparoscopy as an additional method for staging patients with pancreatic cancer

Surgical management of pancreatic cancer

P. Chervenkov, R. Radev and H. Georgiev *Department of Surgery, Medical University, Varna, Bulgaria*

Four hundred and sixty-nine patients with pancreatic cancer were reviewed, 316 males and 153 females, mean age for males 62·1 years, for females 66·2 years Analysis of the results suggests a slender chance for early diagnosis because of the delay of first visit of the patients to a doctor and their complex examination, and also late clinical manifestation. Most common signs and symptoms were obstructive jaundice, weight loss, pain, dyspepsia Most important for the exact diagnosis were CT scan, US, ERCP, percutaneous transhepatic cholangiography, and MRI Distribution according to clinical stage was stage I two, stage II 63, stage III 279, stage IV 125 Four hundred and twenty-five were surgically treated The following procedures were performed radical operations in 62 (14·6 per cent), palliative in 291 (68·4 per cent), exploration in 72 (16·9 per cent) The type of resection was Whipple procedure in 29 with postoperative mortality of 13·3 per cent, four patients with fistulas, pancreatoduodenal resection (PDR) with occlusion of pancreatic duct in 27 patients with postoperative mortality of 7 4 per cent without fistulas, pylorus preserving PDR in two patients and total pancreatoduodenectomy in four Mean survival was 18 3 months, 5-year survival was 3 9 per cent Palliative operations were. biliodigestive anastomosis (BDA) in 241 (63 4 per cent), BDA + gastrojejunostomy in 49 (10 4 per cent) Most commonly performed BDA was choledochoduodenostomy in 278 (95 5 per cent), with postoperative morbidity of 9·7 per cent and mortality of 5·8 per cent Mean survival in patients after palliative procedures was 9 7 months

Diagnosis and treatment of intraductal mucin-hypersecreting neoplasms of the pancreas

G Costamagna, M. Marrocco Trischitta, M. Mutignani, D. Frontera and F. Crucitti *Istituto di Clinica Chirurgica, Università Cattolica del Sacro Cuore, Policlinico A. Gemelli, Largo Gemelli 8, 00168 Rome, Italy*

Intraductal mucin-hypersecreting neoplasms (IMHN) are a distinct group of rare pancreatic exocrine tumours characterized by intraductal growth and copious production of mucus that causes dilatation of the main or branch ducts and excretion of mucus through the papilla of Vater.

We report on eight cases of IMHN (six males, two females, mean age 69 1 years, range 41–85 years), diagnosed between 1990 and 1995, in order to discuss the diagnostic reliability of different imaging modalities and the therapeutic strategies for IMHN Seven neoplasms were localized in the pancreatic head and one in the tail Patients presented with recurrent pancreatitis (five cases, 62·5 per cent) or pancreatitis-like symptoms (two cases, 25 per cent) due to temporary complete occlusion of the main duct by viscous mucus, one of them developed pancreatic insufficiency with diabetes as a late sequela of permanent duct occlusion Another patient had an acute cholangitis due to common bile duct stone

At ultrasound and computed tomography dilatation of main or branch ducts and cysts were noted or suggested in seven patients (87 5 per cent). No distant metastases were detected. At endoscopic retrograde cholangiopancreatography (ERCP) a wide open papilla filled with mucus was observed in five patients (62·5 per cent). Cannulation of the papilla showed a dilatation of the main pancreatic duct in six patients (75 per cent) with ductectatic features in four cases and calcifications in two cases Endoscopic treatment, including pancreatic sphincterotomy (four cases) and insertion of naso-pancreatic drainage (four cases) and pancreatic stent (one case), provided extrusion of mucus from the papilla and improvement of symptoms.

Three patients were operated on. pancreatoduodenectomy was performed in two cases and resection of the tail in one case The postoperative course was uneventful in all cases Histologically, a well differentiated adenocarcinoma was diagnosed in one patient whereas no atypia were detected in the other two cases A follow-up of 4·0 years, 3·0 years and 1·8 years, respectively, revealed no sign or recurrence or metastases One 70-year-old patient refused surgery and is still alive and asymptomatic 1 year after endoscopic treatment. Four patients were considered unfit for surgery due to advanced age (>75 years). Three of them died from unrelated causes after 2 months, 3 months and 4 years, respectively, no recurrence of symptoms was noted during the follow-up. One patient was still alive and asymptomatic after 5 years but had had recurrent pancreatitis-like symptoms during the first 3 years.

Our conclusions are· (a) ERCP is the most reliable procedure for proper clinical diagnosis of IMHN, (b) surgical resection should always be performed because of the tendency of IMHN to malignant transformation, (c) endoscopic treatment provides improvement of symptoms in patients in whom surgical resection is considered inadvisable

Acute postoperative pancreatitis

K Dimitrova, V.I. Rachkov and T. Stoyanov *Medical University, 1, St. Kl Ochridski St, 5800 Pleven, Bulgaria*

Early postoperative acute pancreatitis is amongst the most severe of postoperative complications Difficulties in diagnosis and inefficacy of treatment account for a postoperative mortality as high as 50 per cent.

Postoperative pancreatitis was diagnosed after stomach resection according to Bilroth I and II in seven patients, after hepatocholedochotomy in 12 patients, and after other operations in two patients Complications occurred because of (a) postoperative trauma, resulting in digestion disorders, anaemia and hypoproteinosis; (b) after haemorrhage, (c) disturbed immunological mechanisms and neoplasms, (d) in duodenostasis, etc

The diagnosis was based on the history, as well as on clinical, laboratory, ultrasound and CAT findings Treatment included medication and surgery Eight patients were operated on Relaparotomy, lavage and drainage were administered Seven patients were laparostomized and conservative treatment was administered Four patients died

Improvements and perspectives in the diagnosis and treatment of pancreatic carcinoma

P. Dinse, U. Sulkowski, S. Maurer, J. Brockmann, G. Winde, F. Pelster and H. Bünte *Department of General Surgery, Westfälische Wilhelms-Universitat, Münster, Germany*

A retrospective study was carried out to evaluate whether any improvements have been made for pancreatic cancer, the most fatal gastrointestinal malignancy, during the last two decades. From 1973 to 1994, 1004 patients suffering from pancreatic adenocarcinoma were treated at the Department of Surgery of Münster University Hospitals: 578 were male and 426 female (sex ratio: 1·4:1). The mean age over the years ranged from 57·4 to 60·2 years. The time from the first symptoms to the diagnosis could be reduced from 4·3 to 3·5 months. Seven hundred and seventeen tumours were located in the pancreatic head. Over the years the rate of curative resections increased from 15·9 per cent to 25·2 per cent. Operative mortality could be reduced from 10·2 to 2·4 per cent The crude 5-year survival rate for patients treated until 1989 was 2·0 per cent, showing a minor improvement. With palliative radiochemotherapy in 45 patients with irresectable tumours we observed a median survival of 15 months Two patients are alive and free of tumour for more than 4 years. Overall, despite a significant reduction of perioperative mortality the general prognosis continues to be very poor. New treatment regimes have to be developed, taking into account that tumours without distant spread a combination of postoperative radiation and chemotherapy can be successful in improving the prognosis.

Analysis of survival following surgical resection of ampullary carcinoma

G.B. Doglietto, D. Frontera, M. Buononato, G. Viola, G. Alfonsi, G. Costamagna and F. Crucitti *Istituto di Clinica Chirurgica, Università Cattolica del Sacro Cuore, Policlinico Agostino Gemelli, L.go A. Gemelli, N° 8, 00168 Rome, Italy*

We evaluated some prognostic factors in 36 patients who underwent surgical resection for ampullary carcinoma (AC). We analysed patient age and sex, tumour size and grading, pTNM stage, extension of surgical resection [Whipple (WR) *vs* pylorus-preserving pancreatoduodenectomy (PPPD)]. There were 21 men and 15 women, whose ages ranged from 39 to 75 years (average 62·1 years). Thirty-five pancreatoduodenectomies (PD) and one subtotal pancreatectomy were performed; eight WR and 28 PPDP were carried out. In all cases lymph nodes along bile duct, hepatic artery, portal vein, superior mesenteric vessels and celiac trunk were dissected en-bloc with peripancreatic tissues. Operative mortality and morbidity were 16 per cent (six patients) and 33 per cent (12 patients), respectively. There were nine stage I, 15 stage II, seven stage III and five stage IV diseases. In nine cases (25 per cent) histological examination showed lymph nodes involvement. Actuarial Survival Rates (ASR) were calculated using the Kaplan–Meier method, excluding operative deaths; statistical analysis was performed using the Cox's test and the Cox's proportional hazard model. Follow-up ranged from 3 to 180 months Overall ASR at 2 and 5 years was 76·7 per cent and 57·9 per cent, respectively Patients with T1–T2 tumours had 2 and 5 years ASR of 82·9 per cent and 65·6 per cent, respectively, while those with T3–T4 tumours had 62·5 per cent and 37·5 per cent, respectively ($P = 0{\cdot}017$) Patients with stages I–II had ASR at 2 and 5 years of 81·3 per cent and 71 per cent, respectively (in this group no tumour recurrence occurred after 5 years), while those of stage III–IV had 2 and 5 years ASR of 70 per cent and 40 per cent, respectively ($P = 0{\cdot}018$), but none survived more than 83 months. Patients with a well differentiated neoplasm had 2 and 5 years ASR of 100 per cent and 87 5 per cent, respectively, those with G2–G3 tumours had 64·7 per cent and 43·6 per cent respectively ($P = 0{\cdot}015$). None of remaining evaluated factors influence survival. Multivariate analysis showed that grading and pTNM stage were independent factors conditioning survival ($P = 0{\cdot}03$).

In our experience survival was significantly related to stage of disease, degree of differentiation of neoplasm and local extension of the tumour, while there were no relationships between tumour size or nodal involvement and survival. Our series shows that PD allows high cure rates in AC, radical lymphadenectomy is always mandatory, regardless of degree of apparent nodal disease, being effective against limited degrees of nodal disease. Moreover there were no survival differences between WR and PPPD: the Traverso–Longmire technique represents an adequate operation for AC.

Traumatic pseudocysts

A. D'Egidio *Department of Surgery, University of Witwatersrand, South Africa and European Hospital, Rome, Italy*

We classify pancreatic pseudocysts into three types: post-necrotic type I—associated with acute pancreatitis; post-necrotic type II—associated with an acute attack superimposed on chronic pancreatitis, retention type III—due to chronic pancreatitis and ductal stricture. We report experience with 18 cases of pancreatic pseudocysts, following blunt abdominal trauma, observed between 1986 and 1993. Most of the patients developed their pseudocysts during the convalescent period (range 8–90 days) The diagnosis of pancreatic pseudocyst was established in all patients by computed tomography. Six patients had ERCP. The management of patients with acute pancreatitis at our Institution is initially conservative. The same applies to patients with traumatic pancreatitis when there are no signs of peritonism and a diagnostic peritoneal lavage is considered negative (RCC less than 100,000/ml; WCC less than 500/ml). None of these patients underwent emergency laparotomy. The size of the pseudocysts ranged from 4 to 18 cm with a mean diameter of 8·7 cm. Four patients were successfully treated conservatively (cyst size: 4–6·5 cm) Twelve patients were managed by percutaneous drainage (size: 8–18 cm) with an average of 14 days of drainage. Two patients had distal pancreatectomy for pseudocysts arising from the body and communicating with the duct. No major complications occurred and there were no recurrences. We feel that percutaneous drainage is a valuable option for the treatment of traumatic pancreatic pseudocysts

Malignant pancreatic neurilemoma treated by pylorus-preserving pancreatoduodenectomy

G. Funariu, V. Stancu, C. Pop, M. Petrescu and I.E. Funariu *1st Surgical Clinic, University of Medicine and Pharmacy, 3 Clinicilor St, 3400 Cluj-Napoca, Romania*

Primary malignant neurilemoma is an extremely uncommon tumour of the pancreas. A patient operated on 2 years ago offered the opportunity to review diagnostic features and surgical policy in malignant neurilemoma of the pancreatic head.

A female patient aged 48 years, was admitted into the hospital for pain in upper abdomen, depression, weight loss, upper digestive bleeding and palpable abdominal mass. Standard and Doppler ultrasonography discovered cystic tumour of the pancreas, hypervascularity and irregularity of the tumour wall, infected content (with gas), and close relationship to inferior vena cava. Surgical exploration revealed cystic malignant tumour located in the lower part of the pancreatic head, with invasion and stenosis of transverse duodenum and enlarged peripancreatic lymph nodes. Needle aspiration revealed purulent material. Superior mesenteric vessels, portal vein and caval vein were not invaded. Pylorus-preserving pancreatoduodenectomy with lymphadenectomy was performed. The reconstruction was carried out in the following sequence. end-to-side pancreaticojejunostomy, end-to-side hepatico-jejunoanastomosis and end-to-side duodeno-jejunostomy. Macroscopic appearance confirmed infected cystic malignant tumour with fine fistulous tract communicating to duodenum. Histological examination discovered malignant cystic neurilemoma of the pancreas which invaded duodenal wall, but without lymph nodes metastases. Postoperative course was uncomplicated. Clinical, X-ray, ultrasound and computed tomography scan follow-up revealed good results, without recurrence or distant metastases.

In conclusion, primary malignant neurilemoma of the pancreas may simulate clinically and macroscopically the cystic adenocarcinoma or pancreatic abscess. The diagnosis is established only by histological examination of the tumour. Malignant pancreatic neurilemoma located in the lower part of pancreatic head without involvement of regional vessels and distant metastases may benefit of pylorus-preserving pancreatoduodenectomy

Surgical management of pancreatic pseudocyst

K. Gemos, B. Laopodis, K. Scouras, J. Gemos, S. Ntourakis, J. Tasiopoulos, L. Rissotti and E. Tierris *1st Department of General Surgery, Red Cross Hospital, 1st Erythrou Str, 11526 Athens, Greece*

Pancreatic pseudocysts were once considered to be an unusual complication of acute, chronic and traumatic pancreatitis. The outcome of surgical treatment in 24 patients with pancreatic pseudocysts is described

During the years 1990–1995, 24 patients (mean age 47 years) with pancreatic pseudocyst were treated by external or internal drainage A diagnosis of acute pancreatitis was verified in nine patients, 12 patients had chronic pancreatitis, three had traumatic pancreatitis and one had pancreatitis of unknown aetiology. Fifteen patients were male and nine were female Gallstones were the most important aetiological agent in 13 of the 24 patients, while alcoholic pancreatitis was diagnosed in only six of those with pancreatitis Fifteen patients were treated by surgical drainage or resection and nine patients were treated by observation; one by percutaneous and one by endoscopic drainage. The rest had small cysts and were treated by observation. Spontaneous resolution was observed in three cases. Average pseudocyst diameter was 8·2 cm, with a range of 3 to 19 There was no operative mortality

In general symptomatic pseudocysts are probably best treated with surgical options (internal or resection). Percutaneous drainage was not successful when used as definitive therapy for multiple pancreatic pseudocyst in this study, but internal drainage is the preferred therapy for cysts Patients with chronic pancreatitis who have symptomatic pseudocyst are probably best treated by resection

Bilateral thoracoscopic splanchnicectomy: promising in the treatment of chronic pancreatitis pain

H. Van Goor*, H.C.J.L. Buschel*, W.B. Barendregt* and J.B.M.J. Jansen† *Departments of *Surgery and †Gastro-Enterology, University Hospital, PO Box 9101, 6500 HB Nijmegen, The Netherlands*

Treatment of pain in chronic pancreatitis is troublesome Patients either use longstanding medication (narcotics) or undergo major surgery for pain Thoracoscopic splanchnicectomy has emerged as a new treatment modality for chronic pancreatitis pain. In a small study on unilateral thoracoscopic splanchnicectomy of the greater and lesser splanchnic nerves, results were disappointing The current study was undertaken to evaluate prospectively the effects of bilateral thoracoscopic total splanchnicectomy in patients with chronic pancreatitis

Eligibility requirements included chronic pancreatitis with severe pain unrelieved by standard methods A standard 10-point visual analogue painscale (VAS) was completed by all patients both pre-operatively and at standard intervals postoperatively A detailed analysis was made of the pain medication used both pre-operatively and postoperatively A bilateral thoracoscopic dissection with cautery of all splanchnic nerve tissue present between the level of the fifth and the eleventh thoracic vertebral body was carried out under the same anaesthesia

Between August 1995 and April 1996, 12 patients were treated. All patients required narcotics for relief of pain pre-operatively The median (range) VAS-score was 8 (6–10) pre-operatively Follow-up is complete and ranges from 1 to 9 months. One month after operation, no patient required narcotics for pain relief The median (range) VAS-score was 2 (0–3) 1 month postoperatively. During follow-up, two patients with severe alcohol abuse again required narcotics for relief of abdominal pain which, however, differed from the pancreatic pain they had before The two patients who have been operated on 9 months ago are still pain-free

Bilateral thoracoscopic total splanchnicectomy offers substantial early promise in the therapy of pain from chronic pancreatitis. The ultimate utility of splanchnicectomy awaits long-term follow-up

Pancreatic duct occlusion after pancreatoduodenectomy

G. La Guardia, A. Frena, F. Martin, W. Thaler and S. Imperiale *II Department of Surgery, General Hospital, I-39100 Bolzano, Italy*

From 1984 to 1995, 100 patients have been treated by pancreatoduodenectomy because of a carcinoma of the periampullary region (83 per cent) or because of chronic pancreatitis (17 per cent); 88 patients underwent an original Whipple's procedure, whereas 12 were operated on according to Traverso-Longmire. In each case, however, the duct system of the rest of the pancreas was occluded using synthetic resins (Prolamin or Neoprene) and a pancreato-jejunostomy has not been carried out Sixty-six of these patients were regularly followed by ultrasound examination (on day 6) and by computed tomography (on day 9 after operation) as well as by serial measurements of the volume and of the amylase content of the drainage fluid Two major problems could be evidenced in this follow-up· (a) the fluid collection at the side of the pancreatic section. A fluid collection (mean diameter: 5·6 cm) occurred in 16 patients (24·2 per cent): in nine cases the collection disappeared spontaneously and seven patients developed a pancreatic fistula; (b) the development of a pancreatic fistula Of the remainder 50 patients (75·8 per cent), without collection around the pancreatic section, five developed a pancreatic fistula. To sum up, pancreatic fistula developed in 12 patients (18·2 per cent)· in 10 cases disappeared spontaneously within a mean time of 45 days after operation and only two patients (3 per cent) required a fistulo-jejunostomy has been carried out.

We conclude that pancreatic duct occlusion with exclusion of the pancreatic stump is a safe procedure with good results.

Surgical treatment of pancreatic carcinoma. Our experience over 78 cases

S Gomez Iglesias, R. Estevan, F.J. Del Pino, P. Poves, F. Cortés, M. Borrego and S. Sancho Fornos *Department of General Surgery I, University Hospital 'La Fe', Valencia, Spain*

Aim: To evaluate the response to surgical treatment of pancreatic carcinoma

Methods: We review 78 patients who underwent surgery for carcinoma of the pancreas during a period from January 1995 until December 1996 The most frequent location was in the cephalic area in 82 per cent, with prevalence of males The mean age was 65·6 years, range 28–85 years. Of the cases 70·5 per cent are aged between 60 and 80 years. The treatment has been surgical in all the patients, namely laparotomy in nine (11·5 per cent), palliative surgery in 61 (78·2 per cent) and resective surgery in eight cases (10·3 per cent), of which three were total duodenopancreatectomies and five cephalics The most frequent type of palliative technique was choledocoduodenostomy in 35 cases and hepaticojejunostomy in 10 cases. Twelve patients were submitted to a double diversion (biliary and digestive).

Results: The operative mortality has been 20·5 per cent (16 cases) Postoperative complications were produced in 33 cases (42·3 per cent) with prevalence of renal failure (four cases), anastomotic dehiscences (four cases), hepatic failure in six patients, and wound infection in seven The hospital mean stay was 17·6 days. The global mean survival has been of 15·8 months with the following results: laparotomy, 8·6 months, palliative surgery, 16·3 months, and resective surgery, 21 2 months Actuarial survival is 14 patients, with maximum of 30 and 36 months in two patients submitted to radical surgery

A retrospective review of a consecutive series of 60 pancreaticoduodenectomies

P. Kolh, C Degauque, L. Forthomme, P. Honore, J L. Gielen, E. Hamoir, M. Legrand and N. Jacquet *Digestive Surgery Service, University of Liege, CHU, B-4000 Liege, Belgium*

In order to assess the surgical outcome of pancreaticoduodenal resection, we reviewed the operative technique and postoperative course of 60 patients who underwent a pancreaticoduodenectomy for malignant disease at our institution from 1 January 1989 to 31 December 1995.

There were 32 males and 28 females; the mean age was 61·5 years (range 34–86 years). Indications for resection were pancreatic adenocarcinoma in 45 patients, ampullary cancer in nine, duodenal adenocarcinoma in three, and cholangiocarcinoma in three. The pancreaticoduodenal resection was performed in a curative intent in 54 patients and was palliative in six patients Six patients had a truncal vagotomy A standard Whipple procedure with antrectomy was performed in 54 patients, and a pylorus-preserving pancreaticoduodenectomy in six patients. The portal vein was resected in four patients Standard lymph node resection was performed in 36 patients, and a radical resection in 24. Thirty-six patients had the pancreatic reconstruction performed with a pancreaticojejunostomy and 24 patients had a pancreaticogastrostomy. All but four pancreatic anastomoses were internally stented In the last 26 patients a transhepatic catheter was placed into the anastomed loop in order to decompress both biliary and pancreatic anastomoses. The gastrojejunal anastomosis was performed using only a portion of the gastric section line in the first 40 patients, and with the entire section line in the last 20 patients.

Mortality was 3 per cent· one patient died on postoperative day 1 due to myocardial infarction, and one patient died on postoperative day 14 from sepsis, after reoperation for pancreatic fistula and intra-abdominal abscess This is the only case of pancreatic fistula of the series Overall morbidity was 44 per cent: transient delayed gastric emptying was the major concern in 24 patients (18 in the group with a partial gastrojejunal anastomosis, and six in the terminal gastrojejunal anastomosis group), three patients developed an intra-abdominal abscess (one drained transcutaneously and two requiring surgical drainage), and haemorrhage from gastroduodenal ulcerative disease was observed in eight patients. Six and eight patients developed endocrine and exocrine insufficiency, respectively.

We conclude that. (a) duodenopancreatectomy can be safely performed by a general service with low mortality; (b) the incidence of delayed gastric emptying can be reduced by including the entire gastric section line into the gastrojejunal anastomosis; and (c) a low incidence of pancreatic fistula can be achieved using a stented anastomosis. In this regard, intraluminal transhepatic drainage of the anastomosed jejunal loop may be helpful.

Gastric acidity after pancreaticogastrostomy and pancreaticojejunostomy

I. Kovács*, P. Árkossy*, M. Mahunka† and P. Sápy* *2nd *Department of Surgery and* †*Laboratory Informatics, University Medical School of Debrecen, Hungary*

Aim: The indications of surgery and the operation of chronic pancreatitis with duct abnormalities is a contentious subject The main indication for operation is the intractable pain There are three main types of operation: partial or total resection of the gland, duct drainage, and denervation. There are two main drainage methods in painful chronic pancreatititis: longitudinal pancreaticogastrostomy, which has not spread widely and conventional pancreaticojejunostomy. The aim of our prospective study to measure whether the pancreatic juice released into the stomach had any effect on gastric acidity compared both forms of surgery and evaluate the results of surgical treatment.

Materials and methods: Between 1992 and 1995, 43 patients with chronic pancreatitis were selected for this study, investigated and operated in our Surgical Department. Twenty-two patients underwent pancreaticogastrostomy, seven cases had pancreatico-cysto-gastrostomy and in 14 patients pancreaticojejunostomy was applied when a two-layer-wide anastomosis was created between the pancreatic duct and the antrum or the jejunum loop to relieve the symptoms. A 24-h gastric monitoring was taken on every patient before and 6 weeks after the operation. The patients have received netilmicin prophylaxis before surgery

Results: Following a complete postoperative check up it was found that both types of operations are effective for pain relief (81 per cent), the median pain scores reduced from 115 (30–220) to 35 (10–190) and 125 (40–230) to 45 (5–210) 83 per cent of the patients had no digestive problems due to pancreatic enzyme substitution. The average postoperative weight gain was 3·8kg and 4·3kg The number of diabetic patients increased from nine to 12. There was no perioperative death. Three patients needed reoperations.

Conclusions: According to our statistical evaluation of 24-h gastric pH monitoring test no alteration was detected in gastric pH level in both groups pre- and postoperatively. It might be the lack of activation of the pancreatic enzymes at the anastomotic site by the low gastric pH level and the decreased pancreatic exocrine function. On the basis of pH measuring and evaluated data we can consider the pancreaticogastrostomy, which is a simple and quick procedure, is also a good operation choice to relieve intractable pain in selected patients with chronic pancreatitis associated with duct dilatation.

Pancreaticoduodenal necrosis due to caustic burns

S. Landen, M.H. Wu, L.B.B. Jeng, E. Bardaxoglou and B. Launois *Departments of Surgery Rennes-France, Tainan-Taiwan and Taipei-Taiwan*

Fourteen patients who had undergone extensive foregut excisions for chemical burns extending beyond the pylorus were included in a multicentre retrospective study. Injuries always resulted from massive ingestion of liquid caustics during attempted suicide All patients underwent duodenectomy or pancreaticoduodenal resection and oesophagogastrectomy or total gastrectomy. Immediate biliopancreatic reconnection was performed in 10 patients, with no added morbidity Operative mortality ($n = 7$) was due to uncontrollable septicaemia and only one patient died as a result of surgical complications A trend towards a more favourable outcome was noted in the group of patients operated within 12h of ingestion of caustics, those undergoing a formal pancreaticoduodenal resection (*vs* duodenectomy), and those having immediate biliopancreatic reconnection (*vs* delayed reconnection). Good functional recovery as defined by the ability to feed orally and the preservation of voice function was obtained in two of five long-term survivors. Functional recovery was unpredictable during the acute phase and depended on late scarring of the airway-alimentary tract junction.

In conclusion, the following should be noted:

(a) chemical burns extending beyond the pylorus should not be considered as being beyond surgical recource,
(b) early radical debridement is necessary to save these patients who otherwise face inevitable death;
(c) duodenal necrosis can be managed by pancreaticoduodenectomy followed by immediate biliopancreatic reconnection;
(d) good functional recovery can sometimes be achieved but depends on late scarring of the airway-alimentary tract junction.

Diagnosis and management of pancreatic pseudocysts: our experience

G. Marino, S. Gruttadauria and G. Gruttadauria *Department of Surgery, Division of General Surgery and Surgical Physiopathology, University of Catania, Catania, Italy*

Pancreatic pseudocysts represent, in relation to evolution of diagnostic and therapeutic procedures, an argument of considerable surgical interest

The authors report on six patients observed in the last 10 years The pancreatic pseudocysts in three cases were post-necrotic, in two cases by retention, and in one case post-traumatic. The symptomatology consisted of upper abdomen pain and irradiated to back, vomiting, anorexia and weight loss. In four cases it was possible to palpate a mass in the left part of the abdomen. One patient presented cholestatic jaundice for compression of biliary duct from the pseudocyst In two cases the pseudocyst was on the head of pancreas and on the body-tail in the remaining cases. US, ERCP, CT scan, NMR were carried out preoperatively. The diameter was <5cm in one case, between 5 and 10cm in three cases, and >10cm in two cases. In four cases surgical operation of internal drain (1 cystogastrostomy, 3 cystojejunostomy) was performed and in two cases pancreatic body-tail resection. All patients were submitted to intraoperative US to evaluate the exact localization of the pancreatic pseudocysts and its thickness. Operative mortality was nil.

Although the therapy of pancreatic pseudocysts in the last few years is changing with the development of imaging methodology that now allows the use of therapeutic techniques such as US-endoscopic internal drainage, the results in terms of complications, also documented by recent literature, are still under discussion.

The authors consider that internal drainage is the elective therapeutic management above all in cases of post-necrotic pancreatic pseudocysts on condition that it is performed respecting the usual technical modalities and reserving less invasive managements only for those cases in which the feasable drains by those methodologies, guarantee certain results

Endoscopic medicamentous vagus nerve blockage in the treatment of acute pancreatitis

A. Montvydas, A. Šlepavičius and V. Žindžius *Klaipėda City Hospital, Liepojos str. 15, Klaipėda, 5809, Lithuania*

In cases of acute pancreatitis (AP) especially 1–3 days after onset of disease we use endoscopic medicamentous vagus nerve blockade (EMVB) as an additional method to routine management of acute pancreatitis. The essence of this method is injection of solution of trimecain and alcohol in the muscular–subserosal space of the stomach between cardia and angulus in lesser curvature We have been using this method since 1992 and have performed it in 74 patients with serious forms of AP

Immediately after the blockage, pain disappeared in 24 patients (32 4 per cent), 38 (51·4 per cent) patients felt significant relief of the pain and 10 (13·3 per cent) patients did not feel any significant improvement. We noticed improvement of general state of the patients in first two groups. Five patients from the third group died Pancreatic necrosis and sepsis were the major causes of death We had no mortality cases in the first and second groups The efficacy of treatment was significantly higher statistically in the group of patients who were subjected to EMBV

By reducing the effect of vagus nerve on the pathological process, this method makes it possible to improve the results of treatment of patients with AP and shorten the terms of inpatient treatment This method is more effective at the beginning of the disease, before any destructive process develops in the pancreas.

Intra-peritoneal gabesate-mesilate in experimentally induced acute pancreatitis in rats

I.A. Muttillo, M. Cardi, L. Amadori, R. Petroni, F. Arnone, V. Arsena, R. Maira and A. Bologese *S S. Chrurgia d'Urgenza 3, Istituto I Clinica Chirurgica, Policlinico Umberto I, Universita 'La Sapienza', Rome, Italy*

Twenty Wistar rats weighing 300 g with acute pancreatitis induced by injection of 20 μg/kg s.c of cerulein every hour for 5 h, were randomized to receive peritoneal lavage (PL) with isotonic saline or the same and gabesate-mesilate Twelve hours after the first injection of cerulein, laparotomy was carried out to access the presence of AP and sample peritoneal fluid. At operation a drainage for peritoneal lavage was left in place: continuous 24-h PL by infusion for 15 min, closure of the drainage for 30 min After 20 days all rats were killed. Pancreatic and pulmonary tissue as well as peritoneal liquid were sampled for histological examination and BG, lipase and amylase plasmatic and peritoneal levels AP was induced in 95 per cent of the rats. High plasma amylase and lipase levels were observed. Lipase levels rose 8 h later than amylase. Higher amylase and lipase levels (>44000 mg/dl) correlated with worse histological changes The group treated with gabesate-mesilate showed faster biochemical normalization and lesser degree of histological changes. Two animals died in the PL with normal saline group, none in the gabesate-mesilate group. We can conclude that PL with gabesate-mesilate is more effective than PL with normal saline in the treatment of AP experimentally induced in rats.

Extended pancreatic resection and stapling of the pancreatic stump for cancer: preliminary experience

G Nanni, A. Scotti, G. Rosso, C. Botta, G.F. Balduzzi, P. Demichelis, M Daffara and E. Coppo *General Surgery Division, S. Andrea Hospital, Vercelli, Italy*

Introduction: The surgical treatment of resectable periampullary cancer (head of the pancreas, distal common bile duct and ampulla of Vater) is still a controversial matter: pancreatoduodenectomy (Whipple's operation) or total pancreatectomy The arguments in favour for or against these procedures are the maintenance of endocrine and exocrine function, the avoidance of the risk pancreaticojejunostomy, the operative mortality and morbidity, the oncological radicality as well as the long-term survival
Materials and methods: From 1985 to 1995, 50 pancreatoduodenectomies were performed with the following kinds of management of the pancreatic stump pancreaticojejunostomy in 11 cases (22 per cent), pancreatic stump closure and Neoprene injection in the pancreatic duct in 15 cases (30 per cent), pancreatic duct ligation (in one case external drainage of the duct) and pancreatic remnant stapling with fibrin glue protection and perioperative administration of octreotide in 24 cases (48 per cent) (the last consecutive of the series).
Results: Two patients (18 per cent) submitted to pancreaticojejunostomy, underwent reoperation for anastomotic dehiscence, eight cases (53 per cent) of diabetes in the follow-up and two pancreatic fistulas (13 per cent), which healed in a few weeks, were observed in patients treated with pancreatic stump closure and Neoprene injection in the pancreatic duct; two pancreatic fistulas (8 per cent), which closed spontaneously, developed after pancreatic duct ligation and pancreatic remnant stapling in 24 cases Two deaths (4 per cent), occurred, in the perioperative period, due to severe bronchopulmonary complications.
Conclusions: It appears that the last procedure could reach all the proposed objectives: the maintenance of endocrine function without the risk of pancreaticojejunostomy, and the same oncological radicality and long-term survival The very low perioperative mortality and a good quality of life, in spite of the small number of patients, justify the further use and evaluation of this technique

Diagnosis and treatment of insulinoma

M. Pavlovsky, N Bojko, A. Perejaslov and S. Chooklin
Medical Institute, Pekarska 69, 290010 Lviv, Ukraine

Insulinoma is a wide-spread tumour amongst apudomas. At the same time, the correct diagnosis is established in 30–50 per cent cases Eleven patients with insulinoma were observed The patients ranged in age from 17 to 58 years. Nervopsychiatric character disturbances, which were evinced by scarcity of glucose in brain cells, prevailed in the clinical picture The provocation test with starvation, determination of glucose and C-peptide blood level, catecholamines urea level were used for diagnosis The middle range of insulin blood level was 21·6 ± 4·1 μU/ml, and C-peptide blood level was 18·9 ± 3·7 pg/ml Hypoglycaemia accompanied by high catecholamines urea level was seen in eight patients. Administration of glucagon (1 mg) was used in complex therapy of hypoglycaemic crisis Ultrasonography and computed tomography were used for the topical diagnosis Nine patients were operated on Resection of pancreatic body and tail (3), resection of tail (5) and tumour enucleation from pancreatic head (1) were performed in these patients Tumour size was from 4 to 52 mm Insulinoma was malignant in one case, in others it had an adenomatosis nature The prophylaxis of pancreatitis, and correction of hyperglycaemia are the major factors in the postoperative period. Insulin-dependent diabetes (daily dose of insulin of 18–42 U) developed in four patients during follow up.

A new reconstructive model after pancreaticoduodenectomy: the triple Roux-en-Y by a P loop

G Pescio, A. Casano and A. Cariati *Division of General Surgery, S. Charles Hospital, Bordighera, Italy*

Pancreaticojejunal anastomosis remains the leading cause of morbidity after pancreaticoduodenectomy Once the pancreatic juice is discharged in the gut, enterokinase, an enzyme present in bile, cleaves trypsinogen to form activated trypsin, and pancreatic A phospholipase causes the hydrolysis of biliary lecithin to form lysolecithin, a strong damaging detergent These mechanisms can lead to the formation of peripancreatic abscess and anastomotic leakage

We propose a method of reconstruction after pancreaticoduodenectomy consisting of a double Roux-en-Y on the same jejunal loop without interruption of the mesentery and a third anatomical Roux-en-Y to reconstitute the alimentary tract. The construction of the double Roux-en-Y draining pancreas and bile duct separately, requires a linear stapler 3–4cm from the biliary anastomosis. In this way, by employing the same loop without mesenteric interruption, two functional excluded loops will be obtained.

The rationale of the suggested model lies on the separation of biliary and pancreatic secretions. This makes it possible to avoid a stagnant cul-de-sac coinciding with the pancreaticojejunal anastomosis and to obtain, in the case of a leakage, a purely biliary and/or pancreatic fistula as far as possible. A gastric diversion, by employing the first jejunal limb to rebuild the alimentary way, would be expected to preserve the well known entero-hormonal feedback mechanisms.

99mTc HIDA scans demonstrated the efficiency of the biliopancreatic limbs, showing normal emptying time of the gastric remnant and the absence of radionuclide stagnation or any alkaline enterogastric reflux

Primary idiopathic necrotic pancreatic abscess: change in pathology or unclassified disease?

F. Popa, H. Gilorteanu, V. Strambu, D. Mateescu and V. Constantin *Surgical Clinic, Emergency Hospital 'St. Pantelimon', Sos Pantelimon Nb 340, Bucharest, Romania*

We have reviewed 46 acute pancreatitis operations from the last 3 years from which nine cases of necrosis and abscess were found to have some special particularities

There were found to be young patients (32 to 49 years old), especially females, entering for peritonitic syndromes and to whom the intraperitoneal finding of a necrotic pancreatitis with an abscess was a complete surprise Presentation of symptoms was 4–24h from the start, and no pathological events were found when the history was taken. Excepting one patient in whom a CT exam revealed pancreatic disease, no other biochemical arguments for pancreatic illness were found Therefore, peritonitis or acute abdomen was operated for and, no signs of necrotizing or haemorrhagic pancreatitis were found Abscesses or 'phlegmona' of the gland and always a fluid peripancreatic collection were found Only in two cases a gallbladder stone was found, in the rest no cause leading to the diease could be noted We have always made a supra- and submesocholic removal of the pancreatic capsula, opening at the same time the retroperitoneal space for drainage, we decompressed the bile duct and drained the peritoneum We achieved a good postoperative evolution, with many fewer complications and lower mortality than the abscesses following necrotizing pancreatitis or NHAP itself (mortality two out of nine patients)

We therefore consider that other ways of the pancreas becoming infected must be found, in the absence of necrosis, that then lead to other forms of disease.

The analysis of factors affecting long-term survival following pancreatic cancer surgery

T Popiela, B. Kędra and D Karcz *1st Department of General and GI Surgery, Jagiellonian University, 40 Kopernika St., 31-401 Kraków, Poland*

Current outcomes of pancreatic cancer surgery are still unsatisfactory, mostly due to the low rates of early pancreatic cancers qualified for surgery The analysis of the most important factors affecting early diagnosis and long-term survival, was carried out in a group of 470 cases (257 females, 213 males) undergoing surgery for pancreatic cancer In 148 patients we performed pancreatic resection (Whipple procedure in 80 cases, Traverso in 29, total in 19, subtotal in 17, segmental in three) In the remaining 322 patients palliative treatment was applied The analysis showed that the most efficient method of diagnosing early pancreatic cancer is performing at least two of the following examinations. USG, ERCP, CT or BAC. The mean survival depends significantly ($P < 0{\cdot}01$) on the tumour size, its localization, lymph node engagement, the presence of distant metastases, vessels infiltrations and the volume of blood transfused in the perioerative period.

The quality of life after surgery for chronic pancreatitis

Z. Puchalski, J.R Ladny, J. Barczyk and J. Laszkiewicz
Department of General Surgery, Medical University of Bialystok, ul. M. Sklodowskiej-Curie 24a, Bialystok, Poland

Chronic pancreatitis is well known as a chronic, progressive disease often accompanied by complications that may require surgical intervention. The affected patients should have adequate therapeutic planning and long-term follow-up.

Aim: To evaluate the quality of life with patients with proven long-lasting advanced chronic pancreatitis The clinical and psychological status of 189 patients who had undergone various surgical procedures for their disease was evaluated. The presence and severity of pain was assessed using Huskisson pain scale. Exocrine and endocrine pancreatic function were measured typically. Nutritional status of patients was also evaluated Depressive disorders were tested using the Zung scale.

Results: Using the Huskisson visual analogue scale to measure pain, 11 (5·8 per cent) patients described their pain as moderate, 34 (17·9 per cent) as mild, 144 did not complain of pain The exocrine pancreatic function was evaluated as impaired in 129 patients (68 per cent), mildly impaired in 25 (13 per cent), and not impaired in 35 (19 per cent). The endocrine function was normal in 95 (50 per cent) patients, 23 (12 per cent) were malnourished, 34 (18 per cent) possibly malnourished, and the rest well nourished

Conclusion: It is not possible yet to prove that surgical treatment for chronic pancreatitis is either more or less likely to induce return to normal life with a high degree of patient satisfaction.

Therapeutic and evolutive aspects of pancreatic pseudocysts

J.J. Resa, L. Arribas, A. Escartín, V. Aguilella, M. Martínez and González *Servicio de Cirugía General 'B', Hospital Clínico Universitario, 50009 Zaragoza, Spain*

Surgical treatment of pancreatic pseudocyst provides definitive management and has a low risk of recurrence, with little morbidity and low mortality. Conservative treatment, in selected patients, has the advantage of low morbidity and mortality, with less discomfort to the patient than a surgical incision

This study reports on the spontaneous and postoperative course in a series of 73 patients with pancreatic pseudocyst; 50 men and 23 women, with mean age of 51·7 years (range 11–77 years). The aetiology was alcohol abuse in 35 (47·9 per cent), biliary tract disease in 31 (42·4 per cent), and a variety of other causes in the remaining seven (9·5 per cent) Echography shows a sensitivity of 88·36 per cent and a specificity of 48·2 per cent Computed tomography has a sensitivity of 89 6 per cent and a specificity of 80 per cent Average pseudocyst diameter was 16·7cm, with a range from 6 to 20cm Conservative treatment was done in 27 patients and it was successful in 22 (81·5 per cent). Surgical treatment was applied to 46 patients and consisted of internal drainage of the pseudocyst in 37 (pseudocystojejunostomy in 12, pseudocystogastrostomy in 10 and pseudocystoduodenostomy in six) and external drainage in 13 and pancreatectomy in five. The 30-day mortality ratio was 8·6 per cent. With a mean of follow-up of 46 5 months, only two recurrent pseudocysts have been found.

The balance suggests that conservative and surgical treatments are useful in different patients Pseudocysts management should be tailored to each individual case

Immunomodulation with interferon-gamma in acute pancreatitis in a rat model

A. Richter, T. Nebe, F. Fiedler, J. Schmoll and S. Ockert *Chirurgische Klinik, Klinikum der Stadt Mannheim, Theodor-Kutzer-Ufer 1–3, 68167 Mannheim, Germany*

In order to test the immunomodulation of interferon-γ, pancreatitis was induced by sodium-taurocholate in male Brown–Norway rats. The study consisted of four groups: Group A ($n = 10$), control, healthy, non-treated animals, without surgical intervention; Group B ($n = 10$), pancreatitis induced, no IFN-γ injection; Group C ($n = 8$), pancreatitis induced, injection of 1·0 ml PBS (phosphate buffered saline) pH 8·0; on post-surgical day 3, 4, and 5; Group D ($n = 10$) pancreatitis induced, injections of 1·0 ml recombinant rat IFN-γ (Fa. Laboserv, Giessen) 200,000 U/mg, on post-surgical day 3, 4, and 5 Pre- and postoperatively blood tests were performed and examined in flow-cytometry The diagnosis of induced pancreatitis was substantiated by enzyme-activity of serum amylase We were able to simulate the so-called 'immunoparalysis' of patients with acute pancreatitis in this model of sodium-taurocholate induced pancreatitis in rats (a) A reduction of HLA-DR expression on monocytes was observed in all animals. (b) Furthermore, the acute pancreatitis in the rat is characterized by leucocytosis, thrombocytosis ($P < 0\cdot001$) and an elevation of neutrophile granulocytes ($P < 0\cdot001$). Besides, we noted a lymphopenia ($P < 0\cdot001$), a reduction of T-lymphocytes ($P < 0\cdot05$), activated T-lymphocytes and a decreased CD4-cell count ($P < 0\cdot001$). (c) Next to these non-specific immunological alterations of a pancreatitis, an obvious increase in serum amylase activity served as evidence of an induced pancreatitis. The latter, however, was decreasing at the end of the observation time interval. (d) Already after the first injection of recombinant rat IFN-γ (20,000 U/mg), a significant increase in HLA-DR expression on monocytes was observed in Group D ($P < 0\cdot001$). (e) During the course of IFN-γ treatment there was an additional monocytopenia ($P < 0\cdot001$) and a reduction of NK-cells ($P < 0\cdot001$), as a direct result of this treatment. (f) The immunomodulation with IFN-γ to improve HLA-DR expression is possible in acute pancreatitis in animal models.

Changes of cytoplasmic calcium concentration of rat isolated pancreatic acinar cells in acute experimental pancreatitis

J. Shen, Z.P. Wu, H. Xiao, Y.H. Song, M. Liu and X.L. Yan *Department of Surgery, Sichuan Continuing Education College of Medical Sciences, Chengdu City 610041, China*

Recent studies indicate that calcium channel blockade could improve pancreatic circulation, limit prostaglandin imbalance and influence the development of acute experimental pancreatitis These findings suggest that the influx of calcium ions may play an essential role in the pathophysiology of acute pancreatitis (AP). Acute experimental pancreatitis was inducted by biliopancreatic retrograde injection of 4·5 per cent sodium taurocholate solution (0·1 ml/30 s/100 g) in 80 Sprague–Dawley rats. Morphological alterations of the pancreas were monitored by histological and ultrastructural techniques With a Shimazu 5000-RF fluorescence spectrophotometer, the intracellular free calcium concentration [(Ca2+)i] of pancreatic acinar cells was measured by fluorescent indicator Fura-2. The results demonstrated that a characteristic feature of early phase of acute necroctic-haemorrhagic pancreatitis was at 2 and 3 h following induction of AP. At 1-,2- and 3-h intervals after the induction of AP, the pancreatic acinar cell (Ca2+)i was increased from sham-operated control 163·04 ± 13·39 nM, 170·08 ± 13·42 nM and 167·46 ± 10·40 nM to 307·19 ± 16·41 nM ($P < 0\cdot001$), 402·75 ± 17·54 nM ($P < 0\cdot001$) and 384·68 ± 33·10 nM ($P < 0\cdot001$) The correlation between the pancreatic acinar cell (Ca2+)i and the severity of pancreatic damages was significant ($r_s = 0\cdot9227$, $P < 0\cdot001$) in the AP group. These data suggest that in the early stage of acute necrotic-haemorrhagic pancreatitis, there existed cell calcium overload in the pancreatic acinar cells Influx of calcium ions may play a key role in the development of bile-induced acute experimental pancreatitis in rats

Management of acute necrotizing pancreatitis

R. Schramm, M. Sykora and H. Thiele *Department of Surgery, Hospital Bruchsal, Gutleutstraße 1/14, D-76646 Bruchsal, Germany*

Acute necrotizing pancreatitis (ANP) is a life-threatening disease. The morality and morbidity still remains high. In the literature different means of treatment are described. When operation is necessary most of the authors favour management of ANP with repeated necrosectomy and drainage of the abdomen.

An evaluation of the patients in our hospital in the time from January 1987 until April 1996 showed 34 cases of ANP requiring surgical intervention. One hundred and sixty-eight patients were treated without operations or just by clearing the common bile duct. Eighty-one major surgical procedures had to be performed In 22 of the 34 cases (64·7 per cent) the pancreas was resected. Only in 12 cases (35·3 per cent) a necrosectomy and drainage was the primary operation. Sole necrosectomy and drainage showed only little success in management of severe ANP In most of the cases these procedures were followed by further operations. Only 11 patients (32·4 per cent) were operated on once Major complications leading to further operations were spreading necroses involving the bowel tract In 15 cases (44·1 per cent) a resection of bowel tract had to be performed and in nine cases (3·7 per cent) this led to an anus praeter Three of the patients (8·8 per cent) died early after 1 to 8 days postoperatively, five patients (14·7 per cent) died between postoperative day 35 and 147 The overall mortality was 23·5 per cent

Compared with results reported in the literature our experience in the treatment of patients with ANP showed that more aggressive surgical management, including resections of the bowel tract in an early stage, provides better results than a repeated necrosectomy and drainage of the acute abdomen.

Shedding of ICAM-1: an escape mechanism preventing effective recognition of target cells in ductal pancreatic carcinoma?

M. Schwab, M. Kroll, B. Rumstadt and M. Trede *Surgical University Hospital Mannheim, Theodor Kutzer Ufer, D-68135 Mannheim, Germany*

Cell surface adhesion molecules are thought to play an important role in cellular immunological reactions. The interaction between leukocyte function-associated antigen (LFA-1) and intercellular adhesion molecule (ICAM-1) is one of several cell adhesion ways A soluble form of ICAM-1 (cICAM) was found in the serum of normal individuals Elevated cICAM-1 expression has been observed in a number of malignant diseases. The aim of this study was to investigate whether the level of cICAM-1 is associated with a higher degree of dissemination in ductal pancreatic carcinoma This would be a sign that circulating ICAM-1 interferes with the host immune surveillance system by blocking the adhesion between leucocyte LFA-1 and membrane-bound ICAM-1. Thus, cICAM may interfere with the host immune surveillance system

Serum samples were collected from patients with ductal pancreatic carcinoma ($n = 29$) and normal individuals ($n = 10$) Levels of circulating ICAM-1 and LFA-1 were measured with commercial ELISA kits (DIANOVA). The mean value of cICAM-1 in 29 patients with ductal pancreatic carcinoma was raised more than two-fold in comparison with normal serum samples. We saw a stage dependent elevation of cICAM The mean value of patients with resectable pancreatic carcinoma (Group 1) was 108·9 ng/ml, of patients with locally irresectable carcinoma (Group 2) 140·5 ng/ml and the mean value of patients with a disseminated ductal pancreatic carcinoma (Group 3) was 208·3 ng/ml Only between Group 1 and Group 3 did we see a statistical difference (t-test, $P < 0\cdot05$) In order to show whether cICAM interferes with LFA-1 we investigated the individual levels of cICAM and LFA-1. The quotient of LFA-1/cICAM-1 showed a statistical significance between Group 1 and Group 3 (t-test, $P < 0\cdot05$) and Group 2 and Group 3 (t-test, $P < 0\cdot05$). The comparison between Group 1 and Group 2 was not statistically significant

According to these results we believe that the shedding of ICAM-1 might represent an escape mechanism in ductal pancreatic carcinoma preventing effective recognition of target cells by effector leukocytes.

Multimodality treatment of pancreatic pseudo-aneurysms

T.F. Tihanyi*, K. Hüttl†, L. Harsányi*, A. Magyar* and L.E. Flautner* **Department of Surgery and †Department of Cardiovascular Surgery of Semmelweis University of Medicine, Budapest, Hungary*

During the course of both acute and chronic pancreatitis severe complications may arise. Pseudocyst formation is very common, but less frequently the development of pseudocysts is associated with lesions of blood vessels that are in close proximity to the pancreas.

Patients and methods: During the period between 1986 and April 1996, 23 patients were found to develop vascular lesions either in the form of haemorrhage into a pseudocyst (seven cases) or pseudo-aneurysm of the gastroduodenal or splenic arteries (15 cases), or of the splenic vein (one case). Diagnosis was established by echosonography (all cases except two), computed tomography (four cases) ERCP (five cases) and angiography (six cases). All patients were operated on

Results: Diagnosis of pancreatic pseudo-aneurysm was established preoperatively in six cases only. One out of these proved to be false-negative (turbulence in the content of the pseudocyst). Gastrointestinal bleeding manifested in nine patients, but in five the pancreatic origin was not considered. For the management of the lesions partial resection of the pancreas (five distal, one duodenum preserving head resection) or ligation of the bleeding vessel with external drainage of the pseudocyst was performed (10 cases). Haemorrhagic pseudocysts were also drained externally with the exception of a cystoduodenostomy and two cystogastrostomies. Intra-operatively moderate bleeding gave some concern (seven cases), while postoperatively pancreatic fistulas developed in eight patients drained externally. All stopped spontaneously. In two cases severe gastrointestinal bleeding occurred postoperatively. Angiography verified the bleeding site to be pseudo-aneurysm of the splenic artery and lesion of the gastroduodenal artery. In both cases embolization of the bleeding vessels provided definitive treatment. No operative mortality occurred, only one reoperation was required for abdominal abscess. The mean follow-up time was 58·1 months (5–96 months). Five patients died of unrelated causes, two patients underwent subsequent pancreatic operation, 67 per cent of the patients are doing well.

Conclusions: It is observed that development of pancreatic pseudo-aneurysm was associated with a longer observation or conservative treatment period (5·8 *vs* 2·8 months). Angiography should be considered whenever severe upper gastrointestinal bleeding occurs in patients with known pancreatic disease and the source of bleeding is obscure In selected cases selective embolization of the bleeding site may provide definitive treatment.

Results of treatment in 155 acute pancreatitis cases

M. Tireli, A. Gurkan and S. Kaçar *SSK Tepecik Training Hospital, İzmir, Turkey*

In the past nine years, we treated 158 acute pancreatitis attacks seen in 155 patients. Acute pancreatitis was found to be related to gallstones, alcohol and other aetiological factors in 100 (64·5 per cent), 15 and eight patients, respectively. No aetiological factors could be identified in 32 (20·6 per cent) cases. Twenty-five of the patients showed severe pancreatitis, while 130 of them had mild pancreatitis. One hundred and thirty patients had mild pancreatitis, their symptoms subsided in 5–7 days by conservative therapy. In mild pancreatitis due to gallstones, symptoms ameliorated with conservative therapy Definitive biliary surgery was performed during the same hospitalization. Other pancreatitis caused by other factors were treated according to their aetiology. Eleven of the 25 severe acute pancreatitis required peripancreatic necrosis debridement and postoperative lavage was performed. Four of these 11 cases needed reoperative debridement of necrosis. The global mortality rate was 5 2 per cent The mortality was found to be 0·8 per cent in mild pancreatitis, and 28 per cent in severe attacks. The mortality rate was 6·0 per cent in gallstone associated pancreatitis, and 3·6 per cent in non-biliary pancreatitis.

Patients hospitalized for acute pancreatitis should be classified for their severity and their aetiological factors immediately and the treatment should be planned according to these criteria

Prognostic evaluation of acute pancreatitis (AP): attempt to create own prognostic classification

M. Trystuła, M. Barczyński, J. Jamski, S. Cichoń, H. Stanuch and W. Hładki *IIIrd Department of General Surgery, C.M. Jagiellonian University, ul. Prądnicka 37, 31-202 Kraków, Poland*

The goal of the study was to attempt to establish the kind of prognostic classification which would utilize only the most significant and AP-specific parameters while, at the same time, monitoring day by day changes.

The collected material, investigated prospectively, included a group of 62 patients with AP, treated in our surgical department, between January 1991 and May 1993. In order to determine the probability of survival of patients with AP in relation to values of estimated parameters and duration of patient follow-up (day 1, 3, 5 and 10) the method of logistic discrimination and regression was used. It was established that chances of survival for patients with AP were significantly affected, during observed days, by four basic indicators of laboratory tests: pO_2, glucose, urea, and calcium; and estimation of clinical state, by means of· pulse rate measurements, and subordinating the score count to that of Trapnell's classification as well as one-time utilization of data referring to patient age, aetiology, morphological form of AP, incidence of complication and concomitant diseases. To all of the prognostically significant parameters the value ranges were established and the appropriate point count were allotted depending on their values. The total score of the points obtained for the above parameters is estimating the state of health of patients with AP on day 1, 3, 5 and 10 of follow-up. The usefulness of the new scale for prognosis of survival of patients with AP was verified and then compared, for the same patients with the values calculated to Ranson and Imrie's method. The present scale, utilized in appropriate time sequence, allows for current monitoring of the course disease part from the possibility of giving a prognosis of appropriate survival. The proposed method, in comparison to Ranson and Imrie's method, presents a higher prognostic probability, while the number of estimated laboratory indicators remains lower.

Classification	Sensitivity (per cent)	Specificity (per cent)	FVD* (per cent)	FVS* (per cent)	TCC* (per cent)
Own	93	62	67	91	87
Ranson	83	50	38	89	77
Imrie	58	58	23	87	58

*FVD – predictive value of death, FVS – predictive value of survival, TCC – total correct classification.

Estimating resting energy expenditure in a group of hospitalized patients with pancreatic cancer

D. Venskutonis and R. Šiugžda *2nd Clinic of Surgery, Kaunas Medical Academy, Kaunas, Lithuania*

When indirect calorimetry facilities are unavailable, various predictive formulas are used to estimate resting energy expenditure (REE) According to our opinion these predictive formulas are inaccurate in a group of pancreatic cancer patients To assess the accuracy of these formulas we examined prospectively the ability of above-mentioned formulas to predict REE in such patients, undergoing surgery.

Dietary recall, body weight, biochemical nutrition assessment and anthropometric data were collected and indirect calorimetry performed in 19 male and six female patients, aged 27–70 years Mean body weight was 62·2 (49–104) kg. The predictive formulas consistently underestimated by between 6·1–16·4 per cent and were poorly correlated with mean REE as measured by indirect calorimetry.

	Mean REE (kcal/day)
Indirect calorimetry results	1635·3
Robertson–Reid Formula	1367·6
Fleisch Tables	1431·0
Boothy *et al* Formula	1478·9
Aub–Du Bois Formula	1535·3
Harris–Benedict Formula	1422·8

In a group of hospitalized pancreatic cancer patients conventional predictive formulas are inaccurate. When indirect calorimetry facilities are unavailable in such patients, the Aub–Du Bois Formula may be useful in predicting REE

Pancreatic duct occlusion (PDO) with fibrin sealant (FS) for the protection of the pancreatic-digestive anastomosis

H.W. Waclawiczek and O. Boeckl *Ist Surg. Dept. and L - Boltzmann-Institute for Exp./Gastroenterol. Surg., Landeskrankenanstalten Salzburg, A-5020 Salzburg, Austria*

The pancreatic-digestive anastomosis is highly dangerous when a normal pancreatic body after pancreatic head resection has to be anastomosed with the jejunum. In the literature many procedures for the permanent as well as the temporary elimination of the exocrine pancreatic secretion are known which in most cases are responsible for the anastomosis-related complications In animal experiments we could show the efficiency of PDO with FS for the protection of this anastomosis, in the meantime we could gain great experience with this method in clinical trials

Method: Since 1987, 93 patients underwent partial duodenopancreatectomies (Whipple's procedure) due to pancreatic head or peri-ampullary carcinomas After typical pancreatic head resection the duct of the remaining pancreas was intubated with a thin catheter and then occluded with an average of 2(±0·4) ml FS A high concentration of aprotinin (antifibrinolytic substance) of 20,000 IU/ml added to the sealant is required to prevent a premature dissolution prior to postoperative day 5 Then the remaining pancreas was anastomosed in single-layer fashion

Results: The postoperative mortality rate amounted to 2 1 per cent (n = 2) and was not method-related In three cases bile fistulas occurred, in one a partial liver necrosis and in another one a colonic necrosis, which required relaparotomies. No pancreatic fistulas occurred A remarkable fact is that postoperatively only five of the patients suffered from exocrine and only three from endocrine, insulin-dependent insufficiencies.

Conclusion: The PDO with FS represents a safe and effective method for the protection of the pancreatic-digestive anastomosis and can therefore be recommended for Whipple's procedure

Mucin antigen expression and biological behaviour of the pancreatic and intrahepatic bile duct carcinoma

S. Yonezawa, K Sueyoshi, M. Nomoto, M. Higashi, M Taira, Y. Arimura and E. Sato *Second Department of Pathology, Kagoshima University School of Medicine, 8-35-1 Sakuragaoka, Kagoshima 890, Japan*

The aim of this study was to evaluate what types of mucin antigens are correlated with the biological behaviour of neoplasms in the pancreas and intrahepatic bile duct.

Immunohistochemically, expression of MUC1 and MUC2 mucin antigens was examined in 18 invasive tumours with poor outcome (10 invasive ductal carcinoma of the pancreas, eight cholangiocarcinoma) and in 19 non-invasive tumours with favourable outcome (11 intraductal papillary mucinous neoplasm of the pancreas; eight bile duct cystadenocarcinoma). For MUC1, several antibodies for MUC1 mucins of different glycosylation levels were used. For MUC2, in addition to the immunohistochemistry, MUC2 messenger RNA was detected by *in situ* hybridization.

Among several MUC1 mucins examined, the expression of sialylated MUC1 mucin was closely related with the invasive tumours, but the expression of the other types of MUC1 mucins was not related with the invasive tumours The expression of MUC2 mucin, which was usually coincided with MUC2 mRNA expression, was closely related with the non-invasive tumours Actually, all the invasive tumours (18 out of 18, 100 per cent) showed a pattern of sialylated MUC1(+) and MUC2(−). In contrast, many of the non-invasive tumours (15 out of 19, 79 per cent) showed a pattern of sialylated MUC1(−) and MUC2(+). The remaining four non-invasive tumours, which had highly histological atypia, showed a pattern of sialylated MUC1(+) and MUC2(−) likewise the invasive tumours, suggesting that sialylated MUC1 mucin expression seems to be related with malignant transformation of the non-invasive tumours.

These results indicate that the pattern of expression of MUC1 and MUC2 mucin antigens are associated with the biological properties of neoplasms in the pancreas and intrahepatic bile duct, and are useful to predict prognosis of the patients with those neoplasms or to decide the treatment methods for the patients.

Combined method by 'open abdomen' and lumbothomiam in the treatment of infectious necrotizing pancreatitis

B. Zalewski, W. Tołwiński, D. Cepowicz and Z. Kamocki *Department of Gastroenterological Surgery, Medical University of Białystok, 15-276 Białystok, Poland*

The aim of this study is to appreciate various methods of the treatment of seve necrotizing pancreatitis. Pancreatic abscess and infected necrosis of surrounding tissues are the most serious complications of acute pancreatitis. These complications occur in more than 10 per cent of patients Changes in the pancreas and other tissues usually concern the retroperitoneum It seems that in these cases the operation of choice may be 'open abdomen' method combined with the lumbothomiam.

We have operated on 42 patients in our Department in the last 10 years We combined lumbothomiam in addition to 'open abdomen' in eight patients. Three (37·5 per cent) of them died this is less than the percentage in the world literature.

It seems that the operation using 'open abdomen' supported by the lumbothomia may be the way to treat the most serious complications of necrotizing pancreatitis

Vein invasion as an important prognostic factor in renal cell carcinoma

R. Grosso, R. Latino, G. Marino, S. Costa and
G. Vagnoni *Department of Surgery, Division of General Surgery, University of Catania, Catania, Italy*

Renal cell carcinoma (RCC) is a tumour with a remarkable vascular tropism, in fact it is associated in 4–10 per cent of cases with intrarenal and intracaval neoplastic extension, involving the right atrium. In these cases it is necessary to associate a caval thrombectomy with extended nephrectomy. The purpose of this study is to verify if venous invasions can be considered a negative prognostic factor for the development of renal tumour.

The authors report on 200 patients affected by renal cell carcinoma observed from 1985 to 1995. The patients were divided into two groups: Group A included 180 patients with carcinoma without vein invasion; Group B included 20 patients. 12 with renal vein and eight with vena cava invasion (Prichett's type A, B, C). Preoperative study has been carried out with intravenous pyelography, colour-Doppler ultrasound, echocardiography, CT scan, NMR, cavography. In all cases excision of the kidney and the perinephric tissue, adrenalectomy and regional lymphadenectomy has been carried out. In the cases of infrahepatic intracaval neoplastic extension an excision of tumorous thrombus has been carried out after achieving conventional vascular control over the infrahepatic cava vein and opposite renal vein In the cases of retrohepatic intracaval neoplastic extension a radical nephrectomy has been performed with venacavotomy and thrombectomy after Pringle's manoeuvre. In the cases of suprahepatic intracaval neoplastic extension to it a radical nephrectomy has been performed with a bifemoro-atrial partial venous bypass prior to tumour thrombectomy. The 5-year survival was 78 per cent for the patients of Group A and 55 per cent for Group B: no survival difference was demonstrated based on the level of venous involvement On the basis of the obtained results, the authors indicate that venous invasion itself seems to be an important prognostic factor in renal cell carcinoma

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Some conclusions regarding multiple organ failure (MOF) in urosepsis

F. Purcaru, D. Manta, A. Dragusin, A. Grigorescu,
M. Surpateanu, P. Tomescu, M. Rizea, A. Panus, G. Mitroi and
V. Iordache *Clinic Hospital Nr. 1, Intensive Care Unit, Bd. I. Antonescu, Nr. 60, Craiova, 1100, Dolj, Romania*

Aim: We set forth some points of view regarding urosepsis that we have considered to be related with the host's immunological response and not only with a microbial body invasion.

Material: Our study covered 76 urosepsis cases (88·5 per cent men, with 73·7 per cent belonging to the sixth and seventh decade of life) who have developed MOF. Using haemoculture, uroculture and pathological products offered by surgery we have identified different micro-organisms in a variety of proportions and in some cases we have identified another associated disease. The clinical, biological, imagistical data and the histopathological aspect have made the diagnosis of MOF. We have evaluated the clinical form of the organic dysfunction, the gravity and the simultaneous or successive appearance of insufficiency in different organs, the number of the affected organs and the prognosis.

Results: Out of 76 studied patients, 29 (38·1 per cent) have presented only one dysfunction and 47 (61·8 per cent) have presented more than one dysfunction. The most severe multiorganic dysfunctions were: acute respiratory distress syndrome (ARDS), acute renal failure (ARF) and neuropathological disorders which have registered 86·2 per cent mortality rate. More favourable associations of organic dysfunctions there were: ARF + jaundice and ARF + haematological disorders. The mortality rate of the entire group of study was 44·7 per cent. The prognosis was function of the number of involved organs, the gravity of organ dysfunction, the precedent pathology, the age, an exact prophylaxis and therapy of the sepsis condition. We have achieved significant results using Tienam, which present a very large spectrum of action and which has prevented the severe forms of MOF.

Conclusions: (a) Sepsis induced by an urinary disease has led to MOF with a severe prognostic because of an altered ground of the patients (b) Earlier medical and surgical treatment has relieved the MOF through a correct local treatment of the urosepsis; the antibiotherapy function of the involved micro-organism and until the result of antibiogram, the Tienam was very good.

Thoracic

Management of malignant pleural effusion: VATS *vs* 'open' techniques

M. Alloisio, P. Macrì, P.P. Brega Massone, M. Basilico and G. Ravasi *Divisione di Chirurgia Toracica, Istituto Nazionale Tumori di Milano, Milan, Italy*

In our Institute, from January 1989 to January 1996, 235 patients underwent surgery for treatment of malignant pleural effusions One hundred and sixty-eight patients were treated by 'open' techniques and 67 patients underwent video-assisted thoracoscopic treatment. In VATS group 42 patients were male and 25 were female, aged between 29 and 76 years. Histology was lung cancer in 20 cases, malignant mesothelioma in 18, breast cancer in 14 and other different histological types in 15 patients In lateral position, after introduction of camera in VI or VII intercostal space and eventually one or two additional accesses, and after having seen complete pulmonary re-expansion we performed pleurodesis by instillation of talc or alcohol in all pleural recesses. This technique allowed us to practise further surgical procedures such as mediastinal biopsy, pleurectomy and/or pulmonary wedge resections. We compared our data obtained using VATS with a retrospective series of 168 patients treated by 'open'-technique pleurodesis (minimal lateral muscle-sparing thoracotomy and costotomy). We pointed out a reduction of surgical operating time for VATS (35 min) *vs* other techniques (45 min). Postoperative complications were four out of 67 for VATS (two wound infections, two persistent air leakages), and nine out of 168 for 'open' procedures. Mortality was nil in each case. Postoperative chest pain was significantly lower in VATS procedure. The average postoperative hospital stay was 3 days for VATS *vs* 5 days for open thoracotomy A therapeutic success (that we consider when no recurrence of pleural effusion is present after 3 months from treatment) was obtained in 47 (70·1 per cent) patients for VATS *vs* 109 patients (64·9 per cent) for other techniques. From our data we can assume that VATS pleurodesis is to be preferred because of the decrease of surgical operative time, chest pain and time of hospital stay; so we suggest it to be, in future, the treatment of choice for malignant pleural effusions.

Thoracoscopic partial pericardiectomy in the diagnosis and management of pericardial effusion

J.A. Fernández, R. Robles, A. Piñero, F. Acosta, J.A. Lujan, J.A. Torralba and P. Parrilla *Servicio de Cirugía General y del A Digestivo, Hospital 'Virgen de la Arrixaca', 30120 El Palmar, Murcia, Spain*

Aim: To present our experience with thoracoscopy in the diagnosis and management of pericardial effusions.
Methods: Twenty-two partial pericardiectomies were performed with the thoracoscopic approach in patients with pericardial effusion, the aetiology of which was uraemic in seven, neoplastic in eight, idiopathic in five, septic in one and postpericardiotomic in one. All cases had grade III/IV radiological cardiomegaly and ultrasonographic confirmation of the effusion We found haemodynamic compromise in 17 patients The operation requiring the insertion of three trocars, enabled us to remove a large part (6 × 10 cm) of the left anterolateral side of the pericardium and aspirate the effusion
Results: In five cases we found coexisting pleural effusions. The pericardial effusions had a mean volume of 817 ml, which was serous in 11 cases, haematic in six, serohaematic in four, and purulent in one. Cytology was positive for neoplasia in four cases. We observed conversion to grade I/IV cardiomegaly in 16 cases and return to normality in the other six with absence of ultrasonographic recurrence of the effusion after a mean follow-up of 20·5 months (range 2–47 months).
Conclusions: The thoracoscopic management of pericardial effusion is a simple and effective technique that allows us to create a large pericardial window that drains the effusion definitively, determines its aetiology and explores and treats coexisting pleural lesions, all without recurrences.

A 20-year collection of mediastinal tumours

Á. Hrívó, I. Besznyák and F. Pommersheim *Department of Surgery, National Cancer Institute, Ráth Gy. u 7–9, Budapest, 1122, Hungary*

Aim: A retrospective analysis on primary mediastinal tumours of 644 patients of the last 20 years, in order to determine the role of surgery in diagnostics and therapy.
Patients: Interventions were performed with diagnostical or therapeutical intentions. Thirteen per cent of all were thymic tumours, 4 per cent neurogenic, 3·5 per cent teratoid, 4·8 per cent mesenchymal primaries, 27·3 per cent lymphoid manifestations and 20 per cent intrathoracic goitres, 9·3 per cent cystic lesions, 17 6 per cent pseudo-tumours, respectively
Results: It was found that about half of the patients were asymptomatic In the cases of suspected mediastinal tumour all the sophisticated imaging methods were necessary. Open biopsies (conventional mediastinoscopies), VATS or invasive procedures may be therapeutic at the same time. Observation was not the policy. Resection of a primary malignancy was to be attempted in case of technical resectability, except the lymphomas. This was the case for benign tumours as well if the patient was fit for surgery. Non-restricted surgical approach was regarded mandatory for thymic interventions Either patients with uncertain diagnoses or unidentified lesions were referred to as candidates for surgery Surgical approach was always chosen for the special case Surgery generally was the first choice of treatment but multimodality therapy was always taken into consideration
Conclusion: Role of surgery has been unchanged for the last two decades in spite of the developing methods of imaging and multimodality therapy.

Bronchial carcinoid tumours

G. Kontogiannis, S. Moraitis, A. Loutsidis, I. Bellenis, A. Chatzimichalis and N. Exarchos *Thoracic and Vascular Surgery Department, Evangelismos Hospital, Athens, Greece*

Bronchial carcinoid tumours are uncommon neoplasms, and susceptible to surgical treatment Nowadays the width of the excision to obtain the maximal survival is debated

Between 1985 and 1996, 11 patients, seven males and four females, aged 30–67 years old (mean age 49 years) underwent surgical treatment for carcinoid tumour of the lung Recurrent pulmonary infections, haemoptysis and persistent cough were the major clinical features. Two patients were asymptomatic and in another one carcinoid syndrome was present. Chest X-ray manifested central lesions in nine patients and peripheral in two Preoperative diagnosis was established by bronchoscopic biopsy in seven patients. The surgical procedures performed were two left upper lobectomies, three left lower lobectomies, two right upper and middle lobectomies, one right lower lobectomy, one pneumonectomy, two wedge resections while in three patients bronchoplastic procedures were also necessary There were no perioperative deaths. Histological examination revealed only one atypical carcinoid Local recurrence with lymphatic invasion occurred in one patient 3 years after wedge resection and was treated with right lower lobectomy plus chemotherapy. Another patient developed lymphatic invasion 8 years after pneumonectomy and underwent chemotherapy The 5-year survival rate is 100 per cent

Conclusions: (a) Lymphatic invasion adversely affects the prognosis. (b) Complete resection of the tumour is still the primary goal. (c) Surgical techniques preserving lung parenchyma, whenever indicated, have been proved equal to more radical procedures.

Delayed mediastinitis due to secondary oesophageal perforations treated with transoesophageal irrigation

S. Quevedo Losada, L. Lopez Rivero, J. Lopez Pujol, J. Garcia del Caño, N. Betancort, A. Turegano and A. Alvarez Kindelan *Thoracic Surgery, University Hospitals Insular (Las Palmas), and Reina Sofia, Cordoba, Spain*

The purpose of this study is to investigate the treatment of delayed mediastinitis secondary to oesophageal injury (MSEI), with a pseudoconservative approach.

We studied six patients with MSEI during the past 5 years (five males and one female, with an age range of 45–61 years, mean = 57 years). Oesophageal perforation was cervical in two cases and thoracic in the remaining, all instances involved iatrogenic aetiology (two anastomotic cervical leaks and four postoesophagoscopy). MESI was suspected and confirmed by means of an oesophageal contrasted radiological study, with an average delayed time greater than 48 h The treatment included thoracotomy, in the thoracic cases, and wide mediastinal debridement Location of the perforation with refreshment of the wound and 32 Fr drains in the vicinity of the lesion and in the thoracic cavity In patients who could not swallow, oesophageal irrigation was performed through the nasogastric tube. Additionally, when oral intake was possible, the patient would drink only water A percutaneous gastrostomy was performed. Cervical cases were treated in a similar fashion with cervicotomy and cervical drains Evolution was good in five cases with sepsis control and proper healing of the oesophageal perforation. We kept the drains for an average time of 14 days. We registered one case of postoperative dysphagia secondary to tertiary waves and it was resolved with medical treatment. One patient died on postoperative day 1 due to sepsis.

We conclude that mediastinal debridement and oesophageal irrigation is a good therapeutic alternative in cases of delayed MSEI diagnosis.

Thymoma: predictors of survival

M. Martelli, G. Cardillo, R. Giunti, M. Lopergolo, S. Treggiari and F. Facciolo *Department of Thoracic Surgery, C. Forlanini Hospital, Rome, Italy*

Aim: Thymomas are uncommon neoplasm with an incidence of around 70 cases per year in Italy. The purpose of the present paper is to present a modified histological classification and to determine the predictors of survival following surgical resection of thymomas.

Methods: Between January 1990 and April 1996, 38 patients with an histologically proven diagnosis of thymoma were studied. There were 26 males and 12 females, with a mean age of 52 years (range 22–76 years). Six patients (15·8 per cent) were asymptomatic at presentation with a mass on chest radiograph. The most common presenting complaints were cough (34 per cent), dyspnoea (31 per cent), chest pain (28 per cent) and superior vena caval syndrome (8 per cent). Four patients (10·5 per cent) had myasthenia gravis. As regards histological classification we propose, according to preliminary reports of Rosai and Delgado, a modified Salyer-Eggleston: predominantly lymphocytic thymomas (12 cases), predominantly epithelial thymomas (six cases), mixed lympho-epithelial thymomas (four cases), spindle cell thymomas (eight cases), and thymic carcinomas, also called malignant thymoma type II (eight cases). According to Masaoka classification there were: stage I. 16 cases, stage II: four cases, stage III 15 cases, stage IV A· three cases. Operative approach was median sternotomy in 36 cases and posterolateral thoracotomy in two cases. In addition to operation, the majority of patients underwent radiation therapy, chemotherapy or both. Three patients with invasive thymomas underwent, in the last period of our experience, neoadjuvant treatment including both chemotherapy and radiotherapy. The mean follow-up was 44 months (range 3–79 months) Survival analysis was performed by the method of Kaplan–Meier. Significance was defined as a P-value less than 0·05

Results: No patient died postoperatively. The overall 5-year survival was 45 per cent Thirty-one patients (81·6 per cent) underwent radical resection with a 5-year survival of 68 per cent. According to the histological type, spindle cell thymomas and predominantly lymphocytic thymomas had the highest 5-year survival. 83 per cent for spindle cell and 75 per cent for predominantly lymphocytic thymomas The worst prognosis was seen in predominantly epithelial thymomas with only a 30 per cent 5-year survival. One patient with epithelial thymoma underwent thoracotomy for pulmonary metastases 15 months later. According to Masaoka classification the highest 5-year survival was found in stage I (91 per cent 5-year survival).

Conclusions: The modified histological Salyer-Eggleton classification seems to show a good correlation with survival. In agreement with Rosai and Delgado, spindle cell thymomas have the highest 5-year survival while epithelial thymomas have the worst prognosis A good prognosis is also seen in the predominantly lymphocytic group.

Surgical experience in centrally located non-small-cell lung cancer (NSCLC)

E. Mascitelli, F. Santobuono and C. Rapani *Department of General and Thoracic Surgery, University of Chieti, Italy*

Personal experience with lung cancer patients (3451) and related operations (1308) has been reviewed. Of 739 centrally located NSC cases 269 were operated upon Figures of observed cases, explorations and resections are interconnected with different percentage depending on the years considered

Group A included patients observed before the use of better diagnostic procedures: 110 of the centrally located cases went to surgery, but only 29 (26·4 per cent) were resected. Group B consists of cases studied with better TC plus fibre-optic instruments: operations were 127 and resections 85 (67 per cent). Group C is concerned with the last 3 years only, when neoadjuvant therapy was systematically introduced: operations were only 32, *vs* 194 inoperable cases, and resections were 23 (72 per cent)

It is evident as a conclusion that explorations were highly reduced by the possibility of emphasizing local contraindications in advance; and that neoadjuvant therapy seems to open future chances for more resections and possibly for better results

Bronchopleural fistula after pneumonectomy for non-small-cell lung cancer

P.P. Brega Massone, M. Incarbone, L. Tavecchio, C. Gerosa and G. Ravasi *Department of Thoracic Surgery, National Cancer Institute of Milan, Italy*

At our Institute, from 1986 to 1996, 433 pneumonectomies were performed; 159 right and 274 left. Eighteen patients developed a bronchopleural fistula (4·3 per cent) as a complication: eight after right pneumonectomy (5 per cent) and 10 after left pneumonectomy (3·6 per cent). Our series refers to 21 patients, 18 operated in our Institute and three patients who underwent right pneumonectomies in other departments. Twenty of these patients were males and one was female; age ranged between 36 and 72 years, with a mean age of 55·2 ± 9 1 years. Histological findings showed 15 squamous cell carcinoma, five adenocarcinomas and one large cell carcinoma. Nine patients were staged at I, four at II, seven at IIIa and one at IIIb. Five of them received preoperative therapy: radiotherapy in one case, chemotherapy in one case and combined treatment in three cases. In three patients we observed a complete dehiscence of the bronchial stump while in the remaining 19 the fistula was partial, with a mean diameter of 3·6 ± 2·1 mm (range 1–8 mm). Eight patients developed the fistula in the first postoperative period from 2 to 15 days with a mean of 8 ± 4·7 days, while 13 patients developed a chronic fistula between 23 and 1260 days with a mean of 163·5 ± 333. A pleural empyema was associated in 12 cases (57 per cent). In 10 patients we obtained the resolution of the fistula at the first treatment: in seven cases by means of endoscopic therapy with apposition of atossisclerol and tissucol, in two cases by means of a reintervention, with a new suture protected by pericardium or omentum flap, and in one case we obtained a spontaneous closure of fistula by medical therapy and drainage In seven patients we obtained the cure with combined therapy: bronchoscopic treatment and thoracostomy In four cases we did not obtain the closure of the dehiscence: two of these patients died from chronic sepsis and the other two from neoplastic recurrence on the bronchial stump and contralateral metastases. We reported a postoperative mortality from bronchopleural fistula of 23·8 per cent (five patients) To date, seven patients are alive (two with a thoracostomy); seven died of neoplastic disease and two of chronic sepsis We had a 4-year survival of 33 per cent (seven patients) with a mean of 40·7 ± 36·8 months (range 1–116 months)

Isolated aneurysm of the ascending aorta: surgical results and morphological study

X. Mueller*, H. Tevaearai*, C.Y. Genton†, M. Hurni*, P. Ruchat*, A. Fischer*, F. Stumpe* and L. von Segesser*
**Service de Chirurgie Cardio-vasculaire and †Institut de Pathologie, CHUV, 1011 Lausanne, Switzerland*

Aim: The results of repair and replacement techniques in isolated aneurysm of the ascending aorta and the value of histology in predicting the risk of recurrence are analysed

Methods: Between January 1984 and December 1993, 46 consecutive patients were operated on. 27 males, median age 60 years (14–78 years). Four patients had emergency operation for rupture. Repair techniques were applied to aneurysms of less than 6cm, without dissection, annuloectasia, or rupture Of the patients 54 per cent (25/46) underwent aortorrhaphy, with external wall support in four of them, 24 per cent (11/46) had a graft replacement of the ascending aorta, and 22 per cent (10/46) had a Bentall procedure The aortic valve was replaced in 76 per cent of the patients (35/46). The various lesions of the aortic wall were analysed and graded according to the system proposed by Schlatmann and Becker [1]

Results: Hospital mortality was 6 per cent (3/46) two patients had emergency operations. The median duration of follow-up was 5 years (1–11 years) Of the patients 20 per cent of the repair group (5/25) were reoperated on· four who had undergone aortorrhaphy had a recurrence of aneurysm and one who had external wall support had a false aneurysm. Morphological examination revealed extreme variation of lesion severity from one area to another in most cases No reliable predictive morphological parameter for risk of recurrence could be identified.

Conclusions: Aortorrhaphy has a high recurrence rate in comparison with replacement techniques. Histology cannot identify patients at risk of recurrence, therefore intraoperative frozen section would be of no help.

Reference

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Diaphragm traumatism: our experience in 12 years

M.E. Pertejo Muñoz, F. Fernández Ferrero, A. García Muñoz Nájar, A. Sierra García, M. Quadros Borrajos, E. Garrote Nieto, F. Sánchez-Bustos and C. Fernández Monge *Hospital Universitario 12 de Octubre, Carretera de Andalucía, Km 5400 28041 Madrid, Spain*

We review a large group of multiple trauma patients, who present thoracoabdominal injuries, finding 87 cases with traumatic rupture of the diaphragm

We present, in the first place, the mechanism of injury and their associated lesions, which are overall thoraco-abdominal accompany lesions We talk about aetiology, location and classifications (perforations, ruptures, crash, desinsertions, tears, etc.). We expose the clinical manifestations, and the diagnostic approach We mention the surgical procedures, the operative approaches and the treatment of chronic post-traumatic hernia. We show our results and compare them with previous publications.

Videothoracoscopy and minimally invasive surgery for stabilization of traumatic flail chest

D. Di Nuzzo, G. Pieralisi and R. Fulgente *Department of General and Thoracic Surgery, University of Chieti, Italy*

Chest wall injuries with paradoxical respiration require emergency treatment. Different methods are commonly applied to achieve this result· strapping or sand bags when the area is small in size; intermittent positive pressure respiration; surgical fixation using curved struts, intramedullary nails, wires or bone grafts Since 1974 a simple fixation technique was adopted in our Department when exploratory thoracotomy was required two or three Kirschner wires were inserted under the flail segment passing through the intercostal spaces to be positioned outside the upper and lower intact ribs. The same method was used in cases of sternal involvement, with Kirschner wires positioned as in St Andrew's cross behind the sternum From 1990 more conservative methods were applied. in the antero-lateral flail chest positioning of wires was performed by videothoracoscopy only, while in sternal involvement a minimally surgical approach was obtained by a small incision under the xyphoid Among over 1000 cases of chest injuries, 73 patients with flail chest were observed· 44 recovered by conservative methods and 29 required a surgical treatment.

Prognostic value of the histological classification in thymomas with myasthenia gravis

J.M. Ponseti, E. Espín, J.M. Fort, J.L. Sánchez and M. Armengol *Servei de Cirurgía General, Hospital General Universitari Vall d'Hebron, Universitat Autónoma de Barcelona, Barcelona, Spain*

There are several histological classifications currently used to classify thymomas in an effort to grade this tumour. However the value of pathological findings in patients with thymoma and myasthenia gravis is yet to be defined

Aim: To determine the prognostic value of the different histological classifications of thymomas in myasthenia gravis

Materials and methods: We reviewed the files of 88 patients (49 females and 39 males) with myasthenia gravis associated with thymoma. Thymectomies were performed between 1976 and 1993 Median follow-up was 13·4 years Tumour specimens were examined by three different pathologists and staged according to the following histological classifications Salyer (1976), Levine (1978), Masaoka (1981) and Muller-Hermelink (1985). Clinical status prior to operation was according to Osserman's classification stage I (6), II-A (10), II-B (41), III (29) and IV (2). Tumour size ranged from 0·8 to 6·3cm. In patients with invasive thymoma (35), extended thymectomy was carried out, whereas in non-invasive thymomas (53) the tumour along with the thymus gland and its surrounding tissue were excised

Results: The different frequences according to the histological classifications were as follows. Salyer and Eggleston. lymphocytic (11), epithelial (31), mixed (45) and fusiform (1); Levine and Rosai· invasive (35) and non-invasive (53); Marino and Müller-Hermelink· medullary (6), mixed (17), predominantly cortical (25), cortical (37) and well-differentiated thymic carcinoma (3), Masaoka. I (51), II (1), III (33) and IV (3). There were 16 total remissions, 40 asymptomatic with a low dose of medication, 11 with few symptoms and high dose of medication, seven showed worsening symptoms and 14 deaths were detected (one tumour-related and eight disease-related deaths) Clinical outcome of myasthenia gravis showed no statistical differences (χ^2 test) when patients were grouped in the different histological classifications

Conclusions: None of the current histological classification of thymoma has proved to be of prognostic value and none has shown a clear relation with clinical outcome

The omentoplasty for therapy of complicated bronchofistulas

K.J. Walgenbach, M. Kaminski, N.T. Schwarz, J. Jakschik and A. Hirner *Department of Surgery, University of Bonn, Sigmund Freud-Str. 25, 53105 Bonn, Germany*

Introduction: The bronchopleural fistula is a severe complication after pneumonectomy. The mortality rate in a complicated bronchopleural fistula is high. Because of the bradytrophic character of the bronchus the healing process is reduced with a higher risk of insufficiencies. It is known that the transfer of well perfused tissue on to less perfused areas leads to revascularization of the ischaemic tissue For that reason the highly vascularized omentum with a known angiogenic and anti-inflammatory potential as well as a muscle flap are ideal to improve healing in such a problematic area

Methods: From 1994 to 1996 we treated eight patients with a bronchopleural fistula after pneumonectomy. Patients underwent pneumonectomy for cancer (six) or after trauma (two). In the acute phases after the development of a pleural empyema they were treated initially with a thoracoplasty. After stabilizing the patients a pedicled omentum flap based on the right gastroepiploic artery was raised and transposed on to the insufficient bronchus (six), two patients were treated with a muscle flap.

Results: There were no perioperative deaths, three patients developed complications. There was one complication caused by the laparotomy (insufficiency of the abdominal wound). An intrathoracic infection occurred in two patients. In all other cases the primary aim of the operation was achieved without any complications.

Conclusions: The transposition of a well vascularized omentum or muscle flap led to an improved healing in all eight cases of complicated bronchofistulas after pneumonectomy. The angiogenic and anti-inflammatory potential benefits the healing process especially in cases where infection is the predominant problem.

Transplantation

Neuroendocrine effects of orthotopic liver transplantation (OLT) in patients with familial amyloidotic polyneuropathy (FAP)

F Acosta, T. Fuente, R.F. Contreras, P. Ramírez, R. Robles, F.S. Bueno and P. Parrilla *University Hospital 'V. Arrixaca', Murcia, Spain*

Beta-endorphin (Beta-END) is released into the circulation from the pituitary gland in response to various stressful stimuli, including surgery and acute haemorrhagic shock. So far, no studies have been made on the evolution of Beta-END levels during OLT in patients with FAP.

Patients and methods: We studied 22 OLT patients divided into Group A ($n = 8$), patients diagnosed with FAP, and Group B ($n = 14$), cirrhotic patients. Arterial blood samples were obtained at different moments of procedure Beta-END analysis was performed by a solid-phase radioimmunoassay.

Results: Both groups show that preoperative stress and anaesthesia induction do not modify Beta-END levels. However, surgical stress caused a significant increase in the cirrhotics Furthermore, the marked haemodynamic changes caused by vascular clamping and unclamping at the beginning of the anhepatic and neoheopatic phases, respectively, are an additional stimulus for Beta-END release, as it is at these times that the highest levels are attained This did not occur in the FAP patients assessed here, as in most of them the Beta-END levels were lower than the radioimmunoassay sensitivity (4·0pmol/l)

Conclusions: Until now, no patient with FAP has been reported to have central nervous system (CNS) symptoms. However, the absence of Beta-END release suggests a possible CNS disorder, either because the amyloid substance is also deposited here or, simply, because the nerve paths afferent to the brain are affected

The need for immunological manipulation in liver xenoperfusion for fulminant liver failure

M. Adham, J. Baulieux, E. de la Roche, J.M. Sab, C. Ducerf, M. Chevallier, C. Barakat, G. Debize, C. Vianey-Saban, M. Vernet and M. Pouyet *Department of Gastrointestinal Surgery and Organ Transplantation, Hospital de la Croix Rousse, Lyon, France*

Hyperacute rejection is the major obstacle for extracorporeal organ xenoperfusion. A model was used for liver support in patients with acute liver cell failure (ALCF) prior to liver replacement. In this experiment a 31-year-old patient presenting with ALCF on chronic cirrhosis received plasma exchange to correct metabolic errors and blood clotting factor deficiency The collected plasma was reconstituted with packed RBCs and tested in an experimental isolated pig liver perfusion circuit. Changes in blood clotting factors, amino acids, total bilirubin, lactic acid and complement are reported in the table. These results revealed the ability of the pig liver to correct the disturbance in the branched chain to aromatic amino acid ratio (BCAA/AAA) seen in ALCF. Correction of blood clotting factors was deficient for vitamin K dependent factors Decrease in the serum bilirubin level was also noted Levels of C3 and C4 were very low and the level of lactic acid was normal to 11 h after perfusion Histological examination revealed the absence of any sign of hyperacute rejection. This study indicates that the pig liver can correct disturbance in amino acids inherent to ALCF, it also shows the need to supplement the circuit with vitamin K in clinical use. Most interesting is the absence of histological manifestations of hyperacute rejection which can be explained by the very low level of complement in the patient plasma. The need for immunological manipulations prior to pig liver xenoperfusion in patient with ALCF is thus unnecessary.

	T_0	1 h	3 h	6 h	11 h
Total bilirubin (μmol/l)	118	59	56	54	46
PT (per cent)	17	24	24	28	36
Fact V (per cent)	15	42	46	57	73
Fact VII (per cent)	16	5	15	17	21
Fact X	26	27	17	13	14
Fact IX	13	18	10	16	38
Fact XII	14	19	19	32	49
BCAA/AAA	0·57	1·97	1·71	12·9	20·6
C3 (g/l)	0·17	0·19	0·17	0·18	0·19
C4 (g/l)	0·08	0·08	0·08	0·08	0·08
Lactic acid (mmol/l)	6·8	8·1	3·3	1·2	1

Allotransplantation of islet cells in second type diabetic patients

A.A. Alexeyenko, I.E. Verhuletsky, A.G. Osipov and A.A. Slusarev *Medical State University, Donetsk, Ukraine*

Peculiarity of disease in non-insulin-dependent diabetic patients in age from 45 to 62 years with agio- and polyneuropathy complications were investigated The duration of illness was from 7 to 13 years All patients on admission were treated with maximal doses of sugar-reduction drugs, however they had glucosuria, hyperglycaemia, reduction of concentration of insulin and C-peptide in blood plasma The increase plasma cytotoxicity and imbalance of immunity system were also marked For prevention of insulin dependency and progression of complications transplantation of B-cell culture was performed in capsule from greater omentum according to our method Organo-specific floated islet cultures from 20–24 week embrions cultured at 24°C during 7–11 days were used Control examinations after 1, 3, 6, 12 and 18 months transplantation have shown the high efficiency of conducted treatment normoglycaemia, aglucosuria, index of tissue and humoral immunity were stable Fewer patients required sugar-reduction treatment. Thus transplantation of B-cell culture may be used for treatment in second type diabetic patients with successful prevention of insulin dependency.

Thromboxane synthetase inhibitor, UK 38485, ameliorates reperfusion injury in a rat model of kidney transplantation

O Buyükgebiz*, A.O. Aktan†, R Yalm† and M. Dulger* *Department of Surgery, School of Medicine, *Kocaeli University, Kocaeli and †Marmara University, Istanbul, Turkey*

Thromboxane A_2 is a proaggregatory vasoconstrictor that is synthesized and released in reperfusion injury We aimed to investigate the effects of thromboxane synthetase inhibitor (TSI), UK 38485, on endothelin (ET) response of the renal endothelium and lipid peroxidation and protein oxidation and also arachidonic acid metabolism in the early period of kidney transplantation. The groups ($n = 10$) of Sprague–Dawley rats were designed as sham nephrectomy (SNEPH), auto- (AUTO-Tx) and allotransplantation (ALLO-Tx) and ALLO-Tx + TSI. All subjects underwent right nephrectomy after transplantation The grafts were flushed with 4 ml of ice-cold Ringer's lactate and in the latter 10 µg of UK 38485 was added into the solution for each kidney In allotransplantation groups, the kidneys were harvested from allogenic white Wistar albino rats. Grafts were allowed 120 min of reperfusion after 40 min of cold ischaemic period ET-1,2 plasma concentrations in the renal vein blood and diene conjugates (DC), hydroxyalkanals (HAA), hydroxyalkanals (HAE) and malondialdehyde (MDA) levels as the products of lipid peroxidation, protein carbonyls and protein sulphydryls as the indicators of protein oxidation and prostaglandin (PG) E_2 and leukotriene (LT) B_4

levels were analysed in kidney tissue. Plasma ET-1,2 concentrations increased significantly in AUTO-Tx and ALLO-Tx groups ($P < 0{\cdot}05$ and $P < 0{\cdot}01$) when compared to SNEPH but decreased in ALLO-Tx + TSI group in comparison with AUTO- and ALLO-Tx groups ($P < 0{\cdot}05$) DC levels increased in AUTO- and ALLO-Tx groups ($P < 0{\cdot}05$ and $P < 0{\cdot}01$) but HAA, HAE and MDA levels increased only in ALLO-Tx group. Protein oxidation occurred in ALLO-Tx ($P < 0{\cdot}01$) group but did not in AUTO-Tx group ($P > 0{\cdot}05$) Perfusion with UK 38485 prevented lipid peroxidation and protein oxidation significantly ($P < 0{\cdot}001$) in ALLO-Tx + TSI group. The differences in PGE$_2$ and LTB$_4$ levels were not significant and thus revealed that cycloxygenase and lipoxygenase pathways were not involved at this stage. Histopathological changes were less prominent in the last group We concluded that TSI, UK 38485, has a preservative effect and this effect can be related with ET release and/or synthesis rather than arachidonic acid metabolism.

Evaluation of the blood clearance of Tc-99m-HIDA as a test of hepatic function in transplanted livers

F.J. S. Garrido, P. Ramírez, R. Robles, F.S. Bueno, J.M. Rodriguez, J. Luján, M. Miras, J.A. Pons, F. Acosta, A. Piñero, J.M. Marin, T. Fuente and P. Parrilla *Liver Transplant Unit, 'V. Arrixaca' University Hospital, Murcia, Spain*

Aim: To evaluate the blood clearance of Tc-99m-HIDA as a test of hepatic function during the first two weeks after liver transplantation (LT).

Patients and methods: Thirty-three patients were studied: (a) Group 1 (healthy volunteers), 10 cases; (b) Group 2 (transplanted controls) (n = 4), patients after LT with normal liver function tests; (c) Group 3 (transplanted grade I), (n = 10), patients after LT with mild alterations in the liver function tests; (d) Group 4 (transplanted grade II) (n = 7), patients after LT with moderate alterations in the liver function tests and a histological diagnosis of rejection (n = 4) or colostasis (n = 3); and (e) Group 5 (transplanted grade III) (n = 2), patients after LT with severe alterations in the liver function tests.

Results: The blood clearance of Tc-99m-HIDA did not show differences between the healthy volunteers (Group 1) and transplanted livers with normal (Group 2) or mild alterations (Group 3) in the liver function tests. The blood clearance of Tc-99m-HIDA showed statistically significant differences between transplanted livers with normal (Group 2) or mild alterations (Group 3) in the liver function tests and patients with acute rejection or colostasis (Group 4, $P < 0{\cdot}001$) and patients with severe alterations in the liver function tests (Group 5, $P < 0\ 001$).

Conclusions: The blood clearance of Tc-99m-HIDA may be useful as a test of liver function to evaluate situations of clinical relevance after LT.

Portal vein thrombosis after liver transplantation: a review based on a particular case

G. La Greca*, F.W. Schildberg† and H. Denecke‡ **I Clinica Chirurgica Università di Catania, Italy, †Leopoldina KH Schweinfurt, ‡Chirurgische Klinik, Klin. Grosshadern, LMU Munich, Germany*

Portal vein thrombosis (PVT) is the second most common vascular complication following orthotopic liver transplantation. Due to the rarity and subtle clinical manifestations outset for diagnostic measures and therapeutic approach is unclear. Reporting a successful case of long-term survival after re-shunting, using an end-to-side portocaval shunt, for early PVT following liver transplantation, a review of 44 cases of the literature is given. More than 50 per cent of early PVT occur without symptoms. Late PVT is always symptomatic, but the lack of time between thrombosis and symptoms may remain unclear. Mortality is 61 per cent and 6 per cent, respectively, for early and late PVT. No treatment leads to a 100 per cent mortality Endoscopic sclerotherapy was successful in only 35 per cent of all the patients. Post-transplant shunt procedures had a 91 per cent success rate and 0 per cent mortality. If liver function is maintained, early splanchnic decompressive surgery is also important after limited attempt of variceal sclerosing therapy A transplanted liver can maintain a near adequate function without portal inflow. The most important factor to improve the outcome of post-transplant PVT apparently is the splanchnic decompression which may play a role in reducing lethal infectional risk. An aggressive diagnostic and operative approach in post-transplant PVT could greatly improve the results

The use of elderly donors for living related kidney transplantation: 10 years' experience

A. Kostakis, J. Bokos, S. Kyriakidis, D. Stamatiadis, J. Boletis and G. Vosnides *Transplantation Center, Laikon General Hospital, Athens, Greece*

To evaluate the results of renal transplantation from LRD, performed between September 1986 to April 1996, aged over 60 years. Three hundred and eighteen consecutive recipients aged 18–60 years, to whom a kidney was offered by LRD aged 24–82 years, were divided into those whose donors were <60years (Group 1, n = 168, age of donors: 24–59 years, mean: 50·5 ± 7·1 years) and those whose donors were >60 years (Group 2, n = 150, age of donors: 60–82 years, mean: 67·5 ± 5·4 years). Both groups received identical immunosuppression (prednisolone + azathioprine + cyclosporin) Comparison between Group 1 and 2 revealed a statistically non-significant difference regarding the incidence of irreversible acute rejection (five *vs* six patients), permanent loss of graft function due to vascular complications (two *vs* five patients), chronic rejection (13 *vs* 15 patients) and deaths (six *vs* 10 patients) To date (3–110 months post-transplantation), 141 (83·9 per cent) recipients of Group 1 and 114 (76 per cent) of Group 2 continue to have adequate graft function and all donors are alive and well In addition the statistical analysis of biological parameters of graft function at 1, 3 and 5 years post-transplantation, such as serum creatinine, blood urea, proteinuria and hypertension revealed non-significant differences between the two groups. The present study indicates that the results of renal transplantation from LRD >60 years are comparable to those obtained from younger donors.

Therefore, in countries where cadaveric graft donation is poor, LRD age over 60 years should not be ignored and can be used after meticulous assessment of their overall biological status.

Nitric oxide role in mucosa regeneration and in the immune system in rats alloengrafted with an intestinal segment

J. Losada, R. Sarria, R. Jimenez and J. Juarros *Departments of Surgery and Neuroscience, Faculty of Medicine, Hospital Cruces, Basque Country University, Bilbao, Spain*

Nitric oxide synthase immunoreactivity has been evaluated in neonatal bowel segments allografted to adult rats to clarify its role in the bowel mucosae regeneration process, and in the thymus and spleens of these adult animals, organs implicated in specific immunity.

For this purpose, after the isolation of an everted small intestinal segment (ESIS) that was placed subcutaneously, adult rats were alloengrafted with a neonatal small bowel segment. Thirty days later, the nitric oxide synthase immunoreactivity was evaluated in the regenerated intestinal mucosa as well as in the thymus and spleen A quantitative immunohistology study with monoclonal antibodies against CD4 cells, CD8 cells. MHC I and MHC II cells were also made in the thymus and spleen.

A complete recovery of villus architecture exhibiting enterocytes, goblet and Paneth cells with nitric oxide synthase (NOs) immunoreactivity was observed into the lumen of the ESIS. In the small bowel the nitric oxide production is important in minimizing intestinal barrier function in ischaemia reperfusion experiments. In our model, the transplants in which the regeneration process was more difficult showed a more prominent NOs immunoreactivity.

After engrafting, the antigenic stimulus determined a significant increase ($P < 0\ 01$) in the number of NOs immunoreactive cells in the red pulp of the spleen in relation with control values, that could be related with a stimulus for the T-cytotoxic cell proliferation since a significant increase of the CD8 and MHC I immunoreactive cells was observed in the red pulp of engrafted animals

In the thymus of engrafted animals, the number of single cortical positive cells was greatly reduced ($P < 0\ 01$) in relation with controls, being double positive cells (CD4+ CD8+) present in the medulla There was also an enhancement of the number of NOs immunoreactive cells in the cortical area, which production has been related with apoptotic phenomena, that in association with an accelerated lymphoblastic maduration determined a cortical atrophia.

Unrelated living donor grafts and well-matched cadaver donor grafts: a comparative study in renal transplantation

J. Malaise, A. Baldi, P. Setola, M. Mourad, T. Besse, Y. Pirson and J P. Squifflet *Renal & Pancreatic Transplant Unit, University of Louvain Medical School, Brussels, Belgium*

Between 1 May 1983 and 31 December 1994, 39 kidney transplantations were performed using unrelated living donor graft (group ULD) We compared these procedures to 78 cadaver graft transplantations from well-matched donors (group CG), transplanted during the same period and chosen for similar age, sex and graft rank Basic immunosuppressive therapy included cyclosporin, steroids, azathioprine and polyclonal antibodies.

	Group ULD ($n = 39$)	Group CG ($n = 78$)	P
Age (years)	42 ± 10*	41 ± 10*	n s.
Duration of dialysis (months)	18 ± 26*	57 ± 48*	$P < 0\ 000001$
No HLA-A, B mismatches	2·7 ± 1 0*	1·6 ± 1 0*	$P < 0{\cdot}000005$
No HLA-DR mismatches	1·4 ± 0 6*	0·3 ± 0 4*	$P < 0{\cdot}000001$
Cold ischaemic time (min)	191 ± 57	1811 ± 499	$P < 0\ 000001$

*mean ± standard deviation

Patient survival is not significantly different between the two groups (85 per cent at 10 years in group ULD *vs* 81 per cent in group CG, $P = 0{\cdot}28$). Graft survival is not significantly different between the two groups (95 per cent, 81 per cent, 66 per cent at 1, 5, 10 years in group ULD *vs* 90 per cent, 83 per cent, 67 per cent in Group CG, $P = 0{\cdot}45$). Nevertheless, HLA-compatibility is significantly better in group CG. Transplantation of unrelated living donor kidneys in adults are as good with cadaver transplants selected for their good HLA-A, B, DR compatibility. This lack of differences is probably due to a better control on the graft quality, a short cold ischaemic time and a quadruple drug induction regimen begun before transplantation. Furthermore, mean duration of dialysis is shorter in this group.

Serum amylase in heterotopically segmental autotransplantation of the pancreas

C.C. Nikolaou[*], B.E. Papalois[*], A.C. Nikolaou[†], A.E. Papalois[*], N. Galiatsatos[†], G. Bonatsos[*], N. Apostolidis[*], A Andriotis[†] and B. Golematis[*] *[*]First Department of Propeudeutic Surgery, Athens University Medical School and [†]Department of Biochemistry, Hippocration Hospital, 114 Vas. Sophias Ave , GR-115 27 Athens, Greece*

In order to study post-transplant pancreatitis of the segmental pancreatic autotransplantation (right iliac fossa) in the animal model, we used 24 healthy adult mongrel dogs weighing 15·21 ± 2·37kg (mean ± 5·2) and divided them in two groups. a free intraperitoneal drainage group (A) and a duct ligated group (B) and in two subgroups depending on the use (2) of Octreotide 0·05mg b i.d s c. or not (1) Complete biochemical profile was completed preoperatively and on days 1, 3, 10, 30 postoperatively Twenty-four-hour postoperative serum amylase levels rose dramatically in all subgroups (A1: +386 per cent, A2 +278·3 per cent, B1· +492·6 per cent, B2 +333 6 per cent) When the duct was ligated amylase level reached a peak on postoperative day 1 In the free intraperitoneal drainage group, amylase level reached a peak on postoperative day 3 On postoperative day 30, serum amylase had returned to a near-normal level in all subgroups. Octreotide favoured both groups (lower amylase levels) but statistically significant difference was only noticed on postoperative day 3 between subgroups B1 and B2 (10 per cent $> P >$ 5 per cent) and on postoperative day 10 between subgroups A1 and A2 (5 per cent $> P >$ 1 per cent)

	Preoperatively	24h postoperatively	3 days postoperatively	10 days postoperatively	30 days postoperatively
A1	819 4±77 31 $n = 6$	3982 5±1276 2 $n = 5$	4102 3±875 6 $n = 4$	2361 7±475 8 $n = 4$	935 6±236 9 $n = 4$
B1	784 32±122 1 $n = 6$	4653 7±1631 1 $n = 6$	4316 8±932 7 $n = 5$	1447 6±631 8 $n = 5$	894 9±243 3 $n = 5$
A2	832 1±81 67 $n = 6$	3147 7±912 3 $n = 4$	3381 7±617 8	1269 1±298 9 $n = 3$	897 8±133 4
B2	804 16±91 27 $n = 6$	3486 7±1121 8 $n = 5$	2991 7±1082 3 $n = 4$	1073·2±213·4 $n = 4$	833 4±116 7 $n = 4$

Serum amylase level (U/l) (mean value ± s d)
n = living animals

Results and prognostic factors in patients with acute liver failure undergoing orthotopic liver transplantation

R. Robles, P. Ramírez, F.S. Bueno, J.A. Luján, J.M Rodriguez, A. Piñero, J.A. Torralba, J A. Fernández, F Acosta and P. Parrilla *Servicio de Cirugía general y del A. Digestivo, Hospital 'Virge Arrixaca', 30120 El Palmar, Murcia, Spain*

Aim: We present our experience in 17 patients with criteria of acute hepatic failure (AHF), together with morbidity, mortality and prognostic factors.

Patients and methods: Between May 1988 and December 1994 we performed 150 OLTs Seventeen patients (11·3 per cent) presented with AHF, average age was 37 years. Three patients had grade II encephalopathy, seven had grade III and seven presented grade IV encephalopathy. The mean Quick, GPT and bilirubin readings were: 21, 1715 and 22, respectively. Two patients received an incompatible ABO liver The most frequent aetiology was hepatitis of an undetermined origin (seven cases), B virus (four cases), A virus (two cases), C virus (one case), halothane (one case), iatrogenous arterial and portal thrombosis following bile surgery (one case) and acute hepatic failure due to sepsis of an abdominal origin in one patient with Wilson's disease The postoperative medical and surgical complications were analysed

Results: Seven patients died (49 per cent): two from a cerebral origin, four from sepsis and the last patient from a rupture of a pseudo-aneurysm The mortality rate was higher in patients with grade IV encephalopathy than in those with grade II/III. The patients with preoperative complications had a higher mortality rate than those without complications ($P < 0{\cdot}06$), and on analysing each of the complications (renal failure, respiratory insufficiency) we found that the mortality rate was higher but the differences were not statistically significant. The mean survival rate was 35 months (range 14–62 months)

Ultrasonography in the polytraumatized: evaluation of parenchymal injuries that are visable upon admission

P. Cascioli, R. Bonfini, B. Becelli, S Ribaldi, F. Schillaci and M. Coletti *Emergency Surgery Department, 'La Sapienza' University, Rome, Italy*

The objectives in the hospital phase during the 'golden hour' are the stabilization and the early identification, even in unstable conditions, of vital injuries, resulting in a rational and selective diagnosis and therapy In this way the ultrasonography has earned a legitimate place as a non-invasive technique, to verify the clinical objectivity in real time The most reliable diagnostic and simple acquisition criteria is the presence of abdominal free fluid, but it cannot constitute alone a sure and specific condition of necessity for surgical treatment, for this reason ultrasonography's ability to visualize the parenchymal injuries has been studied In order to do that from 1 January 1989 to 31 March 1996, in the department of Chirurgia d'Urgenza and First Aid of the Policlinico Umberto I of Rome, 352 ultrasonographies have been performed on polytraumatized patients within 30 min from admission by the surgeon on duty The clinical characteristics of the patients have been valued according to the ISS (middle value 31), RTS (m.v 5·9), Hb (m.v 12), HT (m.v. 33), FC (m v 90) and PAS (m v 101), furthermore 86 patients presented in a state of shock The first thing we have noticed is the presence of an abdominal injury in 22 per cent of cases The ultrasonography helped to exclude the presence of vital organ injury in 268 cases with an incidence of false-negative of 76·13 per cent, a negative predictive value of 99 per cent and a positive predictive value of 93 per cent The examination furnished five false-positives (1·4 per cent) and two false-negatives (0·6 per cent) Among the 77 cases that were positive, 11 cases (14·3 per cent) were only free abdominal fluid, 29 cases (37·7 per cent) were only parenchymal organ lesion and 37 cases (48 per cent) were both liquid and parenchymal injury. The injuries have involved the liver in 12 cases, the spleen in 34 cases and a kidney in 24 cases In 38 cases (46·3 per cent) a non-operative treatment was decided on for those showing true-positives, 44 patients (53·6 per cent) were operated on, in 12 cases (27·3 per cent) because there was free fluid present (with two cases of false-positives) while in 32 cases (72·7 per cent) there was a parenchymal injury (with two false-positives). The injuries have been correctly evaluated in 48 cases (72·7 per cent), they have been underestimated in 12 cases (18·2 per cent) and overestimated in six cases (9 per cent) The examination furnished a sensitivity of 97 per cent, a specificity of 98 per cent and an accuracy of 98 per cent, data that confirm the full validity and justify its use in the polytraumatized patients The non-completed examinations were 26 (7·4 per cent) with an incidence of false-negative of 0·6 per cent and of false-positive of 0·6 per cent

Abdominal injuries in penetrating thoraco-abdominal trauma

P. Hernández, A. Quintáns, F. Turégano,
M.L De Fuenmayor, M.D. Pérez, G. Chamoso and
J. De Tomás *Emergency Department, H.G U. Gregorio Marañón, C/ Dr Esquerdo 46, 28007 Madrid, Spain*

Aim: To know the efficacy of diagnostic procedures and intra-abdominal injury rate in patients with penetrating thoraco-abdominal injuries.
Materials and methods: From January 1985 to June 1993, all patients with penetrating thoraco-abdominal trauma were included in the study. We registered age, sex, mechanism of injury, localization, clinical situation at admission, type and treatment of thoracic injury, method of abdominal evaluation, surgery indication, abdominal injuries, morbility, reoperations and mortality
Results: Over the study period, 97 patients with penetrating thoraco-abdominal trauma were admitted to the Emergency Department. Ninety-one per cent were men and medium age was 29 years. Stab wound was the most common mechanism of injury (89 per cent). At admission, 36 patients were in shock, three with cardiac tamponade Six patients underwent emergency thoracotomy and 50 needed thoracostomy tube Twenty patients underwent immediate laparotomy for obvious penetrating injury, unstable haemodynamics or clinical signs of peritonitis. In 65 patients, abdominal evaluation were performed by clinical repeated examination in 22 or diagnostic peritoneal lavage (DPL) in 43, as surgeon's choice Missing injury rates were similar in both methods (4·5 per cent and 4·6 per cent) Forty-one patients (42·2 per cent) had abdominal injuries and hepatic and splenic trauma were the most frequent Mortality rate was 4·1 per cent
Conclusions: The rate of intra-abdominal injury in thoraco-abdominal penetrating trauma was 42·2 per cent. Clinical evaluation and DPL are useful to detect injuries, but we must expect missing injury rates of about 3–5 per cent with both

Penetrating cardiac injuries operated on in the general surgery department

A. Kebudi, M. Mihmanlı, A. Isgor and A. Baykan
Department of General Surgery, Şişli Etfal Hospital, Istanbul, Turkey

Penetrating cardiac injuries carry a high risk of mortality and should be diagnosed and treated urgently. Fourteen patients, 13 males and one female, with penetrating cardiac injuries, treated in the Department of General Surgery of the Şişli Etfal Hospital between January 1990 and April 1996 have been assessed The mean age was 31·5 ± 15·2 (18–64) years. All patients were transferred to the hospital by taxis or private cars 20–40 min after the injury. All were stab wounds Signs and symptoms in most patients were hypotension, increase in CVP, muffling of the heart sounds and diminished breathing sounds. Ninety per cent of the patients were operated within 30 min from admission The myocardium was repaired with primary suturing. The pericardium was sutured leaving a hole to avoid retamponade Four patients died peroperatively due to haemorrhagic shock Thus, the mortality rate was 28·5 per cent The mean hospital stay was 14·1 ± 5·0 days In conclusion, for patients with penetrating cardiac injuries, prompt transport to the hospital with appropriate vehicles and medical staff, immediate evaluation and diagnosis of the patient and urgent thoracotomy and primary closure of the heart wounds leaving a hole in the pericardium to avoid retamponade after fluid replacement and resuscitation is very important.

Advanced trauma life support and internet: an Italian experience with Gruppo Aperto per lo Studio del Trauma (GAST)

M. Mongardini, S. Ribaldi, S.M. Calderale and M. Coletti
Emergency Surgery Department, 'La Sapienza' University, Rome, Italy

Internet has become a healthcare community premier site for medicine-related news, information and resources· hundreds of health-care professionals, companies, organizations and consumers use Internet each day. In our experience we are trying to use Websites to update our work in emergency surgery not only in our Department but in the whole town. The purpose of GAST (the initials stand for 'Open Team for Trauma Study') is to bring together all the experiences, knowledge, thoughts. ideas, views and information to improve our healthcare efficiency ability. All of us believe and bring awareness regarding the enormous amount of health-care resources that are available today on the World Wide Web. In particular now we are collecting a lot of experience in· (a) trauma registry [about 700 patients in six years of study with AIS (Abbreviated Injury Score) >16]; (b) operative protocols of health care, (c) prevention and educational programmes; (d) our goal is to have a regional trauma system programme.

Diaphragm trauma: our experience in 12 years

M.E. Pertejo Muñoz, F. Fernández Ferrero,
A. García Muñoz Nájar, A. Sierra García,
M. Quadros Borrajos, E. Garrote Nieto, F. Sánchez-Bustos and
C. Fernández Monge *Hospital Universitario 12 de Octubre, Carretera de Andalucía, Km 5400 28041 Madrid, Spain*

We review a large group of multiple trauma patients, who present thoracoabdominal injuries, finding 87 cases with traumatic rupture of the diaphragm.

We present, in the first place, the mechanism of injury and their associated lesions, which are overall thoraco-abdominal accompany lesions We talk about aetiology, location and classifications (perforations, ruptures, crash, desinsertions, tears, etc.). We expose the clinical manifestations, and the diagnostic approach We mention the surgical procedures, the operative approaches and the treatment of chronic post-traumatic hernia We show our results and compare them with previous publications

Traumatic rupture of thoracic aorta

S. Moraitis, G. Kontogiannis, C. Charitos, E. Apostolakis,
E. Stamataki and C. Lolas *Cardiovascular Surgery Department, Evangelismos Hospital Athens, Greece*

In a 10-year-period (1986–1996) 11 patients, ten males and one female, with a mean age of 31 years, were managed due to traumatic lesion of thoracic aorta All patients were vehicle accident victims (five car drivers, two passengers, four motorcyclists) None of the involved cars was equipped with an air-bag. The trauma involved aortic isthmus in nine cases and the ascending aorta in two cases. The diagnosis was suspected by clinical, chest X-ray and chest computed tomography findings and confirmed by angiography in eight patients In two patients this was confirmed intraoperatively and in one the rupture of the aorta was an autopsy finding. All patients had associated injuries Almost all of them had been hospitalized in other surgical departments or hospitals Therefore, the diagnosis was promptly reached only in one patient (upon admission), while in 10 it was delayed. This delay was fatal for two patients. One patient died 2 h after admission and the other one 12 h after admission in the operating room because of haemorrhagic shock despite surgical efforts. After the establishment of diagnosis all the other patients were promptly operated, except one patient who refused operation. The surgical treatment consisted in graft interposition with the aid of extracorporeal circulation. In the case of ascending aorta trauma a graft interposed and the aortic valve was resuspended Paraplegia, stenosis of the graft anastomosis and chylothorax were the complications of the surgical treatment in three patients, respectively Anastomotic stenosis and chylothorax necessitated a reoperation

Conclusions: Although the prompt diagnosis of the ruptured thoracic aorta is the cornerstone of the management it is usually difficult to achieve. The exclusion of this injury must be one of the first steps in every car accident victim. The use of extracorporeal circulation gives the opportunity of safer surgical manoeuvres.

Traumatic rupture of the diaphragm

C. Neves, P. Coutinho and J. Guerreiro *Department of Surgery, Hospital S.F. Xavier, Lisbon, Portugal*

Aim: Retrospective analysis of 38 cases of acute traumatic rupture of the diaphragm.

Material and methods: The records of 38 patients, who had repair of acute traumatic rupture of the diaphragm during an 8-year period (January 1988–December 1995) were reviewed.

Results: There was a predominance of males (male:female = 4·1.1) The mean age was 37·3 years, ranging from 17 to 81 years Most of the patients (80·6 per cent) had one or more extra-abdominal traumatic injury Penetrating injuries (gunshot and stab wounds) were seen in 20 patients and blunt trauma in the remaining 18 Of the diaphragmatic ruptures 73·6 per cent were in the left side and 26·3 per cent in the right. In three cases there was an associated rupture of the pericardium. All of these patients have been operated on during the initial admission and all by laparotomy We found in 29 patients the following associated intra-abdominal injuries liver 13, spleen 10, small bowel six, colon four, kidney four, stomach three. The global mortality was 7·8 per cent (three cases)

Conclusions: In this series there was a high percentage (52·6 per cent) of penetrating trauma In blunt trauma there was a high percentage (16·6 per cent) of associated rupture of the pericardium Early surgical treatment is indicated in all cases of acute traumatic rupture of the diaphragm to repair the diaphragmatic injury and to treat the associated intra-abdominal lesions that coexist in 76·3 per cent of the patients. The mortality was dependent of the associated traumatic injuries.

Management of diaphragmatic ruptures by trauma: experience in 10 cases

P. Poves, J. Del Pino, M. Meseguer, S. Bonafé, J Silvestre,
C. Herrero, J.L. Ponce and S. Sancho-Fornos *Servicio de Cirurgia, Hospital 'La Fe', Valencia 46022, Spain*

Introduction: The diaphragmatic rupture by trauma has been considered an uncommon entity, with difficult presumptive diagnosis that motivates a lot of therapeutic controversies in the emergency area The production mechanisms in the direct traumatic cases are stab wounds, rib breaks, bull shaft, etc The insidious symptomatology within the polytraumatism context carried to wrong diagnosis covers 60 per cent of the cases, and in the remaining 40 per cent simulates a restrictive respiratory distress and mediastinic oscillation.

Methods: We present a retrospective review of the diaphragmatic ruptures by trauma diagnosed and treated in our hospital in the period between 1991 and 1996 During this period we have operated on emergency basis an overall of 10 diaphragmatic ruptures. Two of them were located on the right side (20 per cent) and eight on the left (80 per cent). The lesions in the first group were an injury by gun shot and the other by stab wound, that produced haemopneumothorax Of the remaining eight cases, five are open injuries (62·5 per cent) and three closed traumas (37·5 per cent) which are in relationship with immediate postprandial period. Associated thoraco-abdominal lesions were: splenic rupture in two cases, one liver laceration, and pulmonary contusion in another patient.

Results: The lesions located on right side were treated with thoracic drainage only and diaphragmatic suture. With respect to type of repair in the lesions of the left side, a primary closing suture in five patients was carried out, and in the other three, a polypropylene graft. In the two cases of splenic rupture, total splenectomy was necessary. There was non-operative morbidity and one postoperative death due to associated brain lesions One subphrenic abscess was referred in one patient, treated successfully by echographic guide-punction Five patients had pleural effusion which did not require punction

Conclusions: Diaphragmatic ruptures should be suspected in all abdominal traumas. This entity requires a differential diagnosis in the emergency area, with the benefit of an early diagnosis and quick surgical treatment. It is very important to explore the abdominal cavity and to find associated thoracic lesions

Value of CT scan in blunt abdominal trauma

A. Quintans, F. Turégano, M.D. Pérez, M.L De Fuenmayor,
J. La Fuente, L. Hernández, J De Tomas and G Chamoso
Emergency Surgery Department, Hospital General 'Gregorio Marañón', C/ Dr Esquerdo 46, 28007 Madrid, Spain

Aim: To assess the value of CT scans which were routinely performed in patients with thoraco-abdominal trauma in our centre

Methods: From 1993 to 1996, 153 thoraco-abdominal CT scans were performed in 238 patients with severe blunt trauma (AIS >2 or ISS >16)

Results: CT scans showed abdominal lesions in 71 patients. Nineteen patients with retroperitoneal lesions (six with a ruptured bladder) and 16 with intraperitoneal lesions (eight with splenic lacerations, three with hepatic fracture and five with intrahepatic haematoma) were treated conservatively. One of the patients with splenic laceration had to undergo a delayed operation for persistent haemorrhage There were two false-negative results (duodenal and jejunal perforation, respectively) and one false-positive (pneumoperitoneum with no findings at laparotomy) The false-negative results were later questioned by a CT scan specialist. Sensitivity was 97 per cent, specificity 98 per cent and accurate rate 98 per cent.

Conclusions: In our experience, CT scan is an excellent method of assessment of blunt trauma patients, with a very low failure rate.

Management of liver trauma

I. Rodriguez. C. Martínez, M. Chames, J. Lesaga, C. Ugena, D. Palomares and E. Bengoechea *Hospital Virgen de la Salud, Avenida de Barber 30, Toledo 45004, Spain*

The purpose of this study is to evaluate the conservative or surgical treatment of the patients that suffered hepatic trauma We have used several scales for this management: Champion's Trauma Score, APACHE II Score and Moore's Scale to evaluate solid viscera injuries We have employed ultrasonography and CT scanning for diagnosis

From January 1990 to December 1994 we have studied 120 patients with blunt abdominal trauma Forty-two of these patients had liver injuries, 18 managed conservatively (CT) and 24 needed surgical treatment (ST). In both groups young males predominated. The most frequent aetiology was a road accident (14 *vs* 18 cases) The mean of scores was TS (13 *vs* 12) and APACHE II (5 *vs* 7). In the CT group all patients suffered minor trauma according to Moore's Scale, and in the ST group minor trauma predominated (21). Intra-abdominal injuries appeared in two and 19 patients. Extra-abdominal injuries were present in 12 *vs* 22 cases, mostly chest (10/17). No patient treated conservatively needed delayed laparotomy. We carried out several treatments in the other 24 cases: 17 haemostatic techniques, seven liver sutures, one right hepatectomy and five cases did not need any treatment. There were eight associated splenectomies in these patients. Only two patients suffered complications in the CT group, whereas 15 patients have some complications in the ST group (10 pulmonary, four renal failure). In the first group one patient needed percutaneous drainage of an intrahepatic abscess. In the other group two patients were reoperated on, one for removal of hepatic packing and the other for intestinal obstruction. The mean hospital stay was 12 *vs* 28 days There was no mortality in either group.

Conclusions: No surgical treatment was possible in selected cases, with controlled bleeding and without other associated intra-abdominal injuries. Non-resective ST is the most frequent surgical management Complications were more frequent in patients with ST and in major injuries $P <$ 0 05)

Has liver injury scale a predictive value on the healing time of non-operatively managed hepatic injuries?

G.A.M. Tiberio*, P. Padalino†, G. Montagnolo*, T. Piardi*, M. Floriani*, S. Bonardelli, A. Pouchè and G. Tiberio*
**Department of Surgical Sciences, Brescia University,*
†Department of Emergency Surgery, Milano University, Italy

Computed Tomography (CT) scaling of the liver injuries revised in 1994 by the American Association for the Surgery of Trauma is precious in the emergency care of injured patients but its predictive value on the healing of conservatively managed hepatic lesions has not yet been assessed. We present the preliminary report of a study designed to evaluate whether healing time correlates or not to the lesion's severity.

Methods: From 1988 to 1995 we admitted 102 patients presenting hepatic traumatic lesions. Thirty-eight of them underwent a non-operative management of 37 blunt and one penetrating (gunshot) injuries. All CT scans were evaluated retrospectively according to the 1994 Organ Injury Scaling: four patients presented grade I lesions, 15 grade II, 13 grade III, five grade IV and one a grade V lesion. Non-operative management failed in one case due to cholepentoneum (grade III lesion). After discharge patients were invited to clinical and echographic controls every 30–60 days, depending on the evolution trend, until the complete healing was demonstrated. Five patients (four grade II and one grade III) refused the follow-up for excessive travel distances and three further patients (all grade III) are currently in follow-up, so there are complete records of 29 patients For statistical analysis we used the Student's *t*-test

Results: No significant healing time differences were observed in regard to the nature of the lesion—haematoma or laceration—in grade I–III injuries Healing time was uniform in grade I injuries and shorter than in grade II lesions (35 ± 9·35 *vs* 69·5 ± 52·9 days, $P =$ n.s.), but a statistical significance was not evident and the recovery pattern was extremely inhomogeneous (range 25–120 days). Healing time was not significantly longer in grade III injuries (86·8 ± 30·4 days) and recovery patterns were very different too (range 55–>180 days). Grade IV–V lesions had the longest healing time (145 ± 102 7 days) but in one case a deep and wide laceration recovered in 30 days and statistical relevance was not evident comparing grade IV–V to grade III, II and also to grade I lesions.

Conclusions: Our data suggest that healing time does not statistically correlate to the lesion severity and that wide deviations from the mean are present in any grade. After discharge every single patient should be submitted to a strict instrumental follow-up to correctly guide progressive return to normal activities.

Is reconstruction in civilian vascular injuries really successful?

M. Zaniewski, K. Ziaja, M. Motyka, L. Cierpka, M. Kazibudzki, M. Tochowicz, E. Majewski, J. Samorodny and T. Urbanek *Department of General and Vascular Surgery, Silesian Medical School, 40-635 Katowice ul. Ziołowa 45, Poland*

The early results of treatment of the vascular injuries are usually satisfactory, but what about the future of the victims? What is their quality of life? The aim of this study is to follow up the patients who have had vascular trauma in the past

Materials and methods: From 1985 to 1994, 379 patients were operated on because of big vessel injuries, among them were 47 women and 332 men. mean age 35 6 years. In 131 (34 6 per cent) patients' injuries included only arteries or veins, in other cases 35·6 per cent nerve injuries were observed, in 38 per cent damages of osteoarticular system Follow-up (1–10 years' observation) were done on 280 (74·8 per cent) per cent Early results showed that limbs of 348 (92 per cent) patients were saved, 22 (5·8 per cent) limbs were amputated, eight (2·1 per cent) patients died. Follow-up indicated that the efficiency of the operated limb was estimated as very good in 78 (27·9 per cent), as good in 136 (48 5 per cent), as bad 66 (23·6 per cent). Two hundred and twenty-two (74·9 per cent) patients' periodically suffered from the complaint connected to the past trauma. The reasons for patients complaints were presented

Conclusions: Early and distal results are usually satisfactory in isolated (arteries or veins) injuries. Long-term fates of victims of vascular trauma are related to concomitant soft-tissue, bone and nerve injuries.

Vascular

Angiomegaly

V. D'Andrea, L. Malinovsky, A. Catania, F. Biancari,
F.M. Di Matteo, A.R. Todini and E. De Antoni
3rd Department of General Surgery, University 'La Sapienza', Policlinico Umberto I, Viale Regina Elena 324, 00161 Rome, Italy

The authors report on a surgical and morphological study on a group of patients with angiomegaly, a vascular disease characterized by elongated and distended vessels affecting the arterial (arteriomegaly) and/or venous system (venomegaly). The arterial group, drawn from a large arteriographic series (1221), includes. (a) megadolicho-arteries, 132 (10 8 per cent); (b) dolichoarteries, 41 (3·3 per cent); (c) megarteries, 26 (2·1 per cent), (d) isolated tortusities, 36 (2·9 per cent), (e) dissecting aneurysms associated with megadolicho-arteries, 19 (1·5 per cent).

The venous group, drawn from a large ultrasound series (703 cases), includes: (a) megaveins with valvular continence, 25 (3·5 per cent), (b) megaveins associated with megadolicho-arteries, 46 (6·5 per cent), (c) megaveins with valvular laxity, 4 (0·5 per cent).

The chief abnormality of angiomegaly seems to lie in a specific alteration of the elastic component of the vessel wall While in atherosclerosis the slow reduction of the lumen takes some years, allowing a viable collateral circulation to open up and come into play on occlusion of the artery, with angiomegaly there is no gradual reduction of flow velocity, so that it becomes complicated with an occlusion of a large artery by segmental thrombosis simulating embolism associated with an insufficient alternative blood supply Results from a large ultrasound study on patients' relatives suggest an inheritance factor in this vascular disease

Leiomyosarcoma of the inferior vena cava: long-term results in five patients

M. Angele, T.U. Cohnert, H.G. Rau and F.W. Schildberg
Department of Surgery, Klinikum Grosshadern, Ludwig-Maximilians-Universitat, Marchioninistr. 15, D 81377 Munich, Germany

Since the first description in 1871 by Perl, a total of 167 cases in the literature have been operated on because of leiomyosarcoma of the inferior vena cava (IVC)

The aim of the study was to determine results of treatment for this rare tumour originating from the vessel wall. Diagnosis of this tumour is difficult because of the lack of specific symptoms.

In the prospective study the data of 5 patients were analysed who underwent surgical treatment for leiomyosarcoma of the inferior vena cava between March 1991 and July 1993. In the three males and 2 females the mean age at time of operation was 52 8 years (range 27–69 years). In two patients curative resection was not possible. One of these patients died 21 days postoperatively, the second 11 months post-exploration and chemotherapy. In three patients resection with curative intent was performed. IVC was reconstructed by direct closure after lateral resection ($n = 1$) or by interposition of a polytetrafluorethylene prosthesis ($n = 2$). All patients developed distant metastases 4 weeks to 25 months after the operation, predominantly in the liver. Despite aggressive chemotherapy the patients died of metastatic disease 16, 39 and 40 months postoperatively without local tumour recurrence The interval between surgery and detection of metastases and the overall survival were not influenced by tumour size, tumour grading according to Coindre or additional therapy. Patients with intravascular tumour growth showed earlier metastases than patients with extraluminal tumour growth

For patients with leiomyosarcoma of the inferior vena cava at the moment surgical treatment is the main approach with curative intent. Multimodal treatment needs further investigation because the overall survival of patients is limited by distant metastases.

Prevalence of varicose veins in the elderly: preliminary report

S. Canonico, F. Campitiello, F. Pacifico, G. Sciaudone, A Bassi and V. Lauletta *Division of General and Geriatric Surgery, Second University of Naples, P zza Miraglia, 80131 Naples, Italy*

The association between increasing age and increasing prevalence of varicose veins (VV) is clearly demonstrated, but only one previous epidemiological study has been aimed at elderly subjects

A large sample of elderly residents in the Region of Campania (Southern Italy) was randomly selected from the electoral rolls for a cross-sectional epidemiological study the group accurately represented the general population The investigation covered 1291 subjects (735 females and 556 males), aged 65 years or more (mean age 74·1 years), who were interviewed and examined in their homes by physicians The following data were recorded age, sex, occupation, body weight, blood pressure, history of VV, constipation, diabetes, congestive heart failure, angina pectoris, previous surgery or other therapy for VV, use of elastic stockings. Data were stored on specially prepared forms and analysed by computer and statistical analysis· a P-value of $<0\ 05$ was chosen as level of significance

VV were more frequent in the >70 years age groups but did not increase significantly with age ($P = 0{\cdot}2355$). The prevalence was 17·6 per cent in men and 38 5 per cent in women with a significant difference, housewives and farmers had significant association with VV. All factors except that diabetes were found statistically associated with the prevalence of VV Of the 388 subjects affected by VV, only 10 (2·6 per cent) had undergone previous surgery and eight (2 1 per cent) had been treated by injection sclerotherapy, 65 patients (16 8 per cent) used elastic stockings with a significant prevalence of not using subjects These data suggest that the prevalence of VV is very high in the elderly Italian population, but often the disease is not treated· perhaps it is superficially supposed that this pathology is not important because the patient is old On the contrary greater attention has to be taken to prevent and care for this disease, that causes much trouble, particularly to elderly patients

Popliteal artery aneurysm: importance of early elective treatment

T.U. Cohnert, H.G Rau, K.L. Lauterjung and
F W. Schildberg *Department of Surgery, Klinikum Grosshadern, Ludwig-Maximilians-Universität Munchen, Marchioninistr. 15, D 81377 Munich, Germany*

The aim of the study was to determine the optimal strategy for treatment of popliteal artery aneurysms (PAA) after their detection

In this retrospective study, the data of 22 patients were analysed who underwent treatment for 23 aneurysms of the popliteal arteries between January 1991 and May 1996 In the 20 males and 2 females mean age was 63·7 ± 11·6 years (range 41–83 years). Mean diameter of the PAA in ultrasonography was 3·1 ± 0·9cm. A unilateral PAA was seen in 16 (10 left-sided, six right-sided) and bilateral PAAs in six. A combination with an abdominal aortic aneurysm (AAA) was present in four (18 per cent) and multiple aneurysms in four, nine were admitted in an emergency situation with acute arterial occlusion Symptomatic arterial occlusive disease (Fontaine Stage IIb) was present in seven. Six were asymptomatic Surgical reconstruction was performed in 19 patients and 20 aneurysms implantation of femoro-popliteal grafts in 18 patients, (seven long. 11 short), and aneurysm resection and direct suture in one with bilateral aneurysms Materials used were autologous vein in seven, PTFE prostheses in six and Dacron prostheses in four. In one exploration revealed no distal reconstruction possibility Two did not undergo surgery in one angiography showed complete occlusion of the distal arterial bed, and one left the hospital without operation There was no operative mortality. Overall morbidity was 30 per cent (6/20 operations) with 9 per cent (1/11 patients) after elective and 56 per cent (5/9 patients) after emergency operation bleeding in one after elective operation, bypass occlusion in one, wound infection in two, urinary tract infection in one. Early reoperations were required in three emergency cases (33 per cent) (amputation in two, bypass occlusion and compartment syndrome requiring five reoperations in one) During the follow-up period (median 24 months) two patients were reoperated because of bypass occlusion after 2 and 4 months

For patients with popliteal artery aneurysms early diagnosis and elective surgical treatment is important because of the high morbidity and amputation rate after emergency procedures.

Intravascular ultrasound control during endovascular interventions: preliminary study

R. Colli*, R. Giudice*, L. Revelli*, A. Cotroneo†, C. Di Stasi†, F. Snider* and V. Di Giovanni* *Scuola di Specializzazione in Chirurgia Vascolare, Istituto di Semeiotica Chirurgica, †Istituto di Radiologia, Università Cattolica del Sacro Cuore, Rome, Italy

Intravascular ultrasonography (IVUS), unlike angiography, can directly visualize both arterial wall and lumen, assessing atherosclerotic plaques characteristics, dimensions and structure. Arterial diameters and cross-sectional areas measurements are more accurate by IVUS than by angiography, especially in severely diseased arteries and in eccentric lesions. The aim of this preliminary study was to evaluate the utility of IVUS control during angiography and endovascular interventions

From November 1995 patients were selected with occlusive arterial disease in the iliofemoral tract that underwent intravascular ultrasound examination during angiography with scheduled endoluminal intervention (balloon angioplasty, stenting). IVUS was performed using 12·5 and 20 mHz mechanical rotating transducers after diagnostic angiography and after any associated endovascular procedure. In our experience IVUS was able to identify arterial wall dissections and intimal flaps not apparent on angiography Ultrasound measurements were more suited than angiographic ones for choosing the right size of endoluminal devices. Intravascular ultrasonography showed residual stenoses and plaque complications after balloon angioplasty whereas the angiographic result was good The technique provided useful information also during stent implantation: in one case an angiographically well-deployed stent turned out to be not completely expanded at IVUS examination

This preliminary study suggests that IVUS can provide accurate measurements and detailed information about arterial wall and lumen as well Intravascular ultrasound control during endovascular interventions can guide the choice of endoluminal devices and assess the effects of the procedure this will probably lead to better short- and long-term results in endoluminal therapy of arterial diseases.

Determining the optimum intermittent pneumatic compression (IPLC) stimulus for lower limb venous emptying using direct pressure measurements

K. Delis*, Z.A. Azizi*, A.N. Nicolaides*, R.J.G. Stevens*, K. Otah*, N. Labropoulos*, G. Stansby* and J.S.P Lumley†
*Academic Vascular Surgery, Imperial College School of Medicine at St Mary's, †Surgical Professorial Unit, St Bartholomew's Hospital, London, UK

Introduction: On the basis of its well documented beneficial effect on arterial calf inflow, and in the absence of established treatment options, impulse technology (IT) is currently emerging as a very potent alternative in the management of intermittent claudication due to PVD. As lower limb veins empty upon compression, the increase of the arteriovenous pressure gradient is thought to play a principal role in augmenting the arterial flow on which the IT action in PVD is based. However, the presets of pressure, impulse frequency and mode (foot, calf or both) of IPLC in the world literature so far have all been selected either arbitrarily or hypothetically.

Aim: To define the optimal selection of mode, least pressure and frequency of IPLC that ensures lower limb venous emptying.

Material and methods: IPLC was produced using the Art Assist A1000 (ACI, San Marcos, CA, USA) Five normal male volunteers, all medical personnel (age range 24–35 years), having no evidence of venous reflux (duplex U/S), were enrolled and six legs were investigated. Lower limb venous pressure in the sitting position was obtained directly, by cannulating a vein on the dorsum of the foot with a 22-gauge heparinized plastic catheter (Ohmeda, Heisingborg, Sweden), connected to an accurately calibrated pressure transducer system (S & W Medico Teknik A/S Alberslund, Denmark). The effect of three IPLC modes [foot (IPFC), calf (IPCC) or both foot and calf (IPFCC)], three frequencies (2, 3, or 4 per min), five pressure levels (60, 80, 100, 120, 140 mmHg) and three delay times (0, 0·5, or 1 sec) was evaluated in all possible combinations (75 different measurements per leg). Investigation of each leg was completed in 2–3 sessions (3–5 h per session). The minimum (P_{min}) and maximum (P_{max}) pressures were obtained between consecutive impulses until a steady state was reached. Pressures are all expressed as the mean of the P_{min} and P_{max}. Statistical analysis was performed using the non-parametric paired Wilcoxon test.

Results: Sitting venous pressure at rest, ranging from 55 to 67 mmHg, decreased to 9–38 mmHg on IPFC (P = 0·036; estimated median of difference = 35 mmHg; 95 per cent CI 25–50 mmHg), to 15·5–31 mmHg on IPCC (P = 0·036; estimated median difference = 36; 95 per cent CI 29–44 mmHg), and to 2–23·5 mmHg on IPFCC (P = 0·036; estimated median difference = 46; 95 per cent CI 37–56 mmHg), under the optimal combination of pressure and frequency for the mode of impulse. IPFCC (delay 1 sec) was more effective then either IPCC (P = 0·036; estimated median difference = 10·5 mmHg, 95 per cent CI 5–14 mmHg) or IPFC (P = 0·036; estimated median difference = 9·75 mmHg; 95 per cent CI 6–15 mmHg). On IPFCC (delay 1 sec) the optimal mean pressure range decreased from 4 to 35 mmHg at two impulses per min to 2–29 mmHg at three impulses per min (P = 0·036; estimated median difference = 4 mmHg; 95 per cent CI 1·75–6·5 mmHg) and was 2–23·5 at four impulses per min (2 *vs* 4: P = 0·036; estimated median difference = 6·5 mmHg; 95 per cent CI 1·8–13 mmHg); and 3 *vs* 4: P = 0·2; estimated median difference × 2·5 mmHg, 95 per cent CI 0·25–6·5 mmHg). On IPFCC a delay of 1 sec was better than 0·5 sec, but no delay was the worst.

Conclusions: In all subjects examined, irrespective of pressure or frequency, the delivery of intermittent pneumatic impulses both to the foot and calf simultaneously, with a calf delay of 1 sec, produced lower venous pressures than either the foot or calf impulses alone Under these conditions a frequency of 3 or 4 impulses per min was always better than 2 per min and a pressure range of 100–120 mmHg was more effective than the 60–80 mmHg range, and equal or just slightly worse than 140 mmHg

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The popliteal artery entrapment syndrome

M. Digalakis, C. Hatziconstantis and A. Rigas Tzanion State Hospital of Piraeus, Glyfada, Athens, Greece

The popliteal artery entrapment syndrome results from a developmental defect through which the artery passes, with consequent compression. We present our experience about this condition which is infrequently described in the literature.

During the last 3 years five young patients were admitted in our surgical department with unilateral claudication in the calf, foot coldness and paresthesias. The abnormality was suspected in all of these patients from the history and the physical examination. Arteriograms were performed which showed medial deviation of the artery and segmental occlusion We operated on these patients with an epidural block. A posterior approach to the popliteal artery was preferred. The procedure was the myotomy (three patients) and myotomy with thrombendarterectomy through a transverse arteriotomy (two patients) There were no complications following the operation and the patients are free of symptoms 3 years later.

Ruptured abdominal aortic aneurysms: 10-year experience in surgical management

N. Exarchos, G. Kalavrouziotis, C. Contrafouris, I. Bellenis, A. Hatzimichalis and A. Loutsidis *Department of Thoracic and Vascular Surgery, 'Evangelismos' General Hospital, Athens, Greece*

Aim: We present a review of our 10-year experience in surgical management of ruptured abdominal aortic aneurysms (RAAA) in order to predict factors improving outcome.

Patients and methods: During the period September 1986 to December 1995, 402 patients with abdominal aortic aneurysm were surgically treated in our department. Of these, 171 patients had an RAAA (42·5 per cent) Sex distribution of the latter was 157 males to 14 females (11·2·1) Their mean age was 68 years (range 42–89 years) The method of surgical management was as simple as possible. minimal tissue dissection and rapid aortic occlusion in different ways, and tubular graft interposition, straight (86 7 per cent) or bifurcated

Results: Perioperative mortality rate was 50·9 per cent (87/171) Causes of death were hypovolaemic shock ($n = 55$, 63 per cent), cardiopulmonary failure ($n = 19$, 21·8 per cent), acute renal insufficiency ($n = 7$, 8 per cent), disseminated intravascular coagulation ($n = 5$, 5·7 per cent), pulmonary embolism ($n = 1$, 1 per cent), and colon necrosis ($n = 1$, 1 per cent). All the survivors postoperatively needed cardiopulmonary support in the ICU A total of 11 reoperations were performed in nine patients (5 2 per cent) due to: acute limb ischaemia ($n = 4$), bleeding ($n = 3$), colon ischaemia ($n = 1$), and retroperitoneal abscess ($n = 1$)

Conclusions: (a) A significant increase in the incidence of RAAA has been observed in the recent decade. (b) Perioperative mortality of RAAA remains high, although it has been reduced in the recent years due to improvement in medical support of the severely ill in well organized ICU. (c) Mortality of RAAA can be further reduced by increased physician awareness and prompt surgical referral

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Value and limits of spinal cord stimulation treatment in critical limb ischaemia: role of the preoperative microcirculatory screening

P. Gersbach, M.G. Hasdemir, F. Mahler and B. Nachbur
University Hospital of Bern, Inselspital, CH-3010 Bern, Switzerland

Aim: To determine the proportion of patients with critical lower limb ischaemia not amenable to surgery or angioplasty that can be treated by spinal cord stimulation (SCS), and to identify potential responders to DCS by a simple test that is sufficiently predictive to limit the need for a trial stimulation period

Design: Twenty consecutive patients with chronic ischaemia threatening one or both lower extremities were assessed by a battery of macro- and microcirculatory tests and by a SCS trial of one or two weeks Favourable response during the trial determined selection for long-term stimulation.

Results: During a 12–29 month (mean 17 months) observation period, limb salvage rate was 63 per cent overall and 83 per cent among patients selected after a favourable trial. Of the tests performed preoperatively, digital substraction angiography, Doppler assessment, laser Doppler flowmetry, oscillometry, capillaroscopy, foot temperature and transcutaneous partial oxygen pressure ($tcpO_2$) in the supine or sitting position did not adequately predict SCS response On the other hand, the supine-sitting $tcpO_2$ gradient ($\Delta tcpO_2$) was a good predictor of SCS outcome, with an 88 per cent limb salvage rate when $\Delta tcpO_2$ was $>$15Torrs, dropping to 12 per cent for $\Delta tcpO_2$ values $<$15Torrs

Summary: SCS is a rewarding therapeutic option in selected patients with refractory critical ischaemic limb disease Base $\Delta tcpO_2$ values appear reliably to predict response to SCS and may obviate the money and time-consuming trial stimulation in most cases.

Lymphatic neoangiogenesis of the omental tissue—a study with the electronic microscope. Prevention of lymphorrhagy in vascular surgery

L. Giacomelli*, L. Leone*, V. Petrozza†, A. Benvenuto†, C. Porcelli*, A. Schioppa*, D. Cecchinelli*, G. Martino* and G. Battisti* **3rd Surgical Department and †Department of Experimental Medicine and Pathology, University of Rome 'La Sapienza', Rome, Italy*

The omentum is used in many different surgical ways· in abdominal surgery for the protection of the anastomoses; in orthopaedics to help the growth of the bone grafts; in cardiosurgery and in neurosurgery to stimulate the vascularization of the ischaemic areas In our group, the omentum is systematically used, in vascular surgery, under the form of free flaps and of pedunculate flaps, generally to protect the anastomoses, and in particular to prevent the lymphorrhagy in the infrainguinal accesses, thanks to the stimulation of the lymphatic neoangiogenesis The prevention of lymphorrhagy allows us to decrease the occurrence of graft infection The omental neoangiogenetic capacity is clearly shown by the research of some authors[1,2] who have isolated two polypeptidic factors from the bovine omentum by a particular biochemical procedure These two factors have a molecular weight of 16·6kD and 18·6kD The aminoacidic composition of the first factor is known. These factors are called FGF (fibroblast growth factor) and ECGF (endothelial cell growth factor).

As regards our clinical experience we have taken into consideration the patient records of the last 4 years (May 1991–December 1995). We have taken into account only the patients who underwent surgical operation for obstructive pathology. For these patients infrainguinal access was necessary to insert the graft. These were 30 consecutive cases (28 males and two females) aged between 48 and 73 years (average 60·5 years) The anastomoses are always protected by the free omental flaps; only in one case we had lymphorrhagy from an infrainguinal surgical wound during the post-operative period which healed within 15 days. At the moment we have had no prosthetic infection. After 6 months we have performed a percutaneous biopsy of the omentum on the patients. The study with optical and electronic microscope has been finalized for the valuation of the changes over the time of the omental graft and to verify the angiogenetic capacity

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Low molecular weight heparins are useful in preventing frostbite lesions

I Gil, A. Guemes, G. Martinez, M.J. Moreno, R. Sousa and J R. Morandeira *Laboratory of Experimental Surgery, Department of Surgery, University of Zaragoza, Spain*

Introduction: Frostbite and its proper treatment are still a clinical problem. Many factors are likely to involved in causing the tissue injury during frostbite (cells injury, endothelium injury, microthrombosis) Low weight molecular heparin has been documented to be useful in avoiding thrombosis An antithrombotic effect of a modified heparin with reduced APTT (activated partial thromboplastin time) has recently been demonstrated in rabbits.

Aim: The aim of the present work was to investigate the effect of a low molecular weight heparin (Enoxaparin) on the microvasculature of tissue suffering frostbite lesions, in an experimental model

Material and methods: Twenty New Zealand white rabbits were allotted to two groups· Group A 10 animals were used as a control A frostbite lesion of the right leg was produced following a model described by our team elsewhere. Group B 10 animals suffered the same experimental model but they were treated with enoxaparin 1mg/kg/day, one day

before and for 5 days after frostbite Animals were anaesthetized with ketamine hydrochloride 50mg/kg body weight injected via i.m. and urethane injected intraperitoneally. We studied leg volume, scar size, skin trophism, amputation level, coagulation tests and microvascular changes.
Results: In the treated group we found a low level amputation (P = 0·0001) comparing with the control group Leg volume was bigger in control group comparing with Group B (P = 0·007) Coagulation tests were modified in the enoxaparin treated group (prolonged APTT). The statistical tests were: Mann–Whitney and Kruskal–Wallis tests. Microvascular changes were a complete thrombosis of dermic vessels in the control group and a lesser degree of thrombosis in the treated group. In this group we also found an integrity of endothelial cells comparing with an almost complete destruction in the control group.
Conclusions: The use of low molecular weight heparin for the treatment of frostbite has proven to be useful in this experimental model allowing lesser tissue damage and low level of tissue necrosis without any severe coagulation decrease.

Intraoperative oxidative stress and free radical injury are associated with higher rate of postoperative complications in thoraco-abdominal aortic aneurysm surgery

H. Hafez, C. Berwanger, L. Hadjinikolaou, A. McColl,
B Richmond, J. Wolfe, A. Mansfield and G. Stansby
Academic Vascular Unit, St Mary's Hospital, Imperial College of Science and Technology, London, UK

Aim: To study the degree and effect of oxidative stress and free radical injury in Thoracoabdominal Aortic Aneurysm (TAAA) Surgery.
Patients and methods: Twenty-one patients undergoing routine Crawford types II and III TAAA repair were studied Arterial blood samples were collected at incision, visceral clamp on, visceral clamp off, 1, 8 and 24h post-declamping. Total plasma antioxidant status (TPAS) and lipid hydroperoxide (Lpx) levels were measured. Major complications were defined as myocardial infarction, arrhythmia requiring treatment, respiratory mechanical support for 5 or more days and renal failure requiring haemofiltration. Data are presented as mean (s e.m.) Wilcoxon signed-rank test was used for correlation between different values.
Results: Mean TPAS at incision was 1·42(0·03)mmol/l During and after surgery levels dropped from the base line values to 1·31(0·03)mmol/l at clamp on (P = 0·007), 1·15(0·04)mmol/l clamp off (P = 0·0001), 1·19(0·05)mmol/l 1h (P = 0·0009), 1·41(0·03)mmol/l and 1·46(0·04) mmol/l at 8 and 24h (P = n s). Lpx levels at incision were 2·21(0·5)µmol/ml, a subsequent biphasic elevation was observed with a first peak of 9·87(2) (P = 0·0005) at clamp off and 5·34(1·4) (P = 0·03) at 1h and a second peak of 4·9(1·1) (P = 0·02) at 24h. Of the 21 patients; nine developed major complications. Those who developed complications had significantly lower TPAS levels at incision and clamp off points than those who did not (P = 0·04 and 0·03, respectively). Likewise, patients who developed complications had significant elevation ot plasma Lpx at clamp off (P = 0·007), at 1h (P = 0·04) and at 24h (P = 0·02), whereas patients without complications had significant elevation only at clamp off point (P = 0·03) In-between groups, Lpx levels were significntly higher in complicated patients at clamp off (P = 0·03)
Conclusion: We conclude that· in TAAA patients there is a significant oxidative stress and free radical injury following splanchnic reperfusion, these changes are particularly prominent in a complicated subgroup of patients with low base line TPAS suggesting that a deficient antioxidant capacity is associated with unfavourable outcome in this group; antioxidant supplementation may be beneficial in ameliorating oxidative stress in TAAA patients

Bioflavonoid quercetin increases nitric oxide level: direct measurements in human endothelial cell cultures

I. Huk*, L. Partyka†, D. Dudek†, G. Weigel‡, V. Brovkovych§,
J. Nanobashvili*, A. Punz*, K. Afkhampour*, E. Roth*,
A. Dembinska†, A. Moibenko§ and L. Polterauer*
**Department of Vascular Surgery, ‡Department of Cardiothoracic Surgery, University of Vienna, Austria,*
†Department of Clinical Biochemistry, CMJU, Cracow, Poland,
§Department of Experimental Cardiology, Institute of Physiology, NASU, Kiev, Ukraine

Successful revascularization of ischaemic tissue is closely connected with reperfusion injury phenomenon Ischaemia-reperfusion injury may be mediated by oxygen derived free radicals. Moreover superoxide radicals avidly destroy nitric oxide (NO) produced by human endothelial cells. Bioflavonoids are known as natural antioxidant substances. Previous studies suggest that water soluble quercetin (wsQ) inhibits lipoxygenase activity and scavenges oxygen radicals (OR)
Aim: Aim of the study was to prove the dose dependent influence of wsQ on NO level in human endothelial vein cell cultures (HUVEC)
Methods: NO generation was directly measured using NO selective electrode. HUVEC were prepared using the modified standard procedure of Jaffe *et al.*, 1973. Cells were cultured in M199 medium containing 20mg/ml fetal bovine serum, 100,000U/l penicillin, 100,000µg/l streptomycin, 100,000U/l low molecular weight heparin and 30mg/l bovine hypothalamic growth factor. The cells were identified as endothelial cells by the typical contact-inhibited cobblestone morphology and by factor VIII (FVIII. vWF) staining. No contamination by myocytes or fibroblasts was detected in the first subculture WsQ was used in following final concentration: 4, 20, 40µM. NO synthase was inhibited by incubation with *N*-nitro-L-arginine methyl ester (L-NAME).
Results: The above doses of wsQ caused significant increase in NO concentration in endothelial cell cultures assessed using the calibration curve. The HUVEC culture rapid release of 24·4nmol NO/500,000 cells after addition of 4µM wsQ in media (peak response), followed by a decrease of NO level for at least 2–3min. This effect was concentration-dependent till 20µM, by application of 20µM of wsQ an NO release of 62nmol NO/500,000 cells was observed, by adding 40µM of wsQ only 46nmol NO/500,000 cells were measured. In contrast the addition of large concentration of wsQ (160µM or more) did not lead to any NO release. Consecutive equal small doses of wsQ caused a kind of cumulative effect. Pretreatment with 1mM L-NAME suppressed the wsQ-induced NO release from HUVEC.
Conclusions: Water-soluble quercetin seems to increases the NO levels in human endothelial cell cultures dose dependently. WsQ may have a certain therapeutic value as an agent capable of promoting natural vasodilatation by low concentrations. We suggest that this effect may be mediated by antioxidant or lipoxygenase-inhibiting properties of the bioflavonoid quercetine.

Endoluminal vascular intervention of renal artery stenosis

L. Inglese, G. Malacrida, E. Onorato and
D.G. Tealdi *Cattedra di Chirurgia Vascolare, Servizio di Emodinamica Ospedale Clinicizzato San Donato, Via Morandi n. 30-20097 San Donato Milanese, Milan, Italy*

Renal artery stenosis can cause renovascular hypertension, renal insufficiency and complicate abdominal aortic surgery. In our institution in the period January 1990 to December 1995, we have treated with endovascular interventional procedures 127 patients, 121 (95 per cent) presenting renovascular hypertension mainly due to stenosis or obstruction of a total of 141 renal vessels Percutaneous transluminal renal artery angioplasty could be performed in 139 of the 141 lesions attempted and completed with implantation of one or more stent in 64 vessels (46 per cent). Immediate angiographic success was achieved in 130 (92 per cent) and major complications were recorded in five patients (4 per cent) One patient (0·8 per cent) died 1 month after complication related to the procedure Two patients required renal artery surgery (elective) for removal of a dislodged stent and one for correction of an axillary vascular complication. Clinical success was recorded in 92 patients (72 per cent) in terms of cure or amelioration of systemic hypertension, and renal function was stabilized in all the patients, except one who presented with serum creatinine over 2·0 mg/dl.

Conclusion: PTRA is a safe and effective procedure to treat renovascular hypertension and stabilize an abnormal renal function due to renal hypoperfusion It can be completed with a high (92 per cent) immediate success, low complication (4 per cent) and low mortality (0·8 per cent)

Intra-operative carotid stent implantation with angioscope control

L. Kollár, L. Horváth, K. Fendler, I. Rozsos, G Kasza and M. Szabó *Department of Vascular Surgery, Baranya County Hospital, University Medical School Pécs, Hungary*

The method of stent implantation is more and more in use in angiology practice The stents introduced by using PTA are employed generally and in large numbers, above all in the femoropopliteal interventions with balloon expansion. The stent implantation with PTA in the area of the carotid has also become more frequent The authors apply intra-operative carotid stent implantation, in the course of which they perform TEA on the arteria carotis communis and the bifurcation with eye-control, then expand the carotis interna with balloon catheter and carry out the stent implantation with angioscope control This method can come into question if the stenosis extends not only to the initial part of the carotis interna, but to a longer section of it.

Revascularization of affected lower extremities via stimulating osteotomy

N L. Kruglov and V.E Zhilin *Department of Vascular Surgery, Region Hospital No 1, Lipetsk, Russia*

The present series is an analysis of treatment of 202 patients with lower extremity occlusive disease (LEOD) in our hospital in the 8 years from 1987 to 1995

All 202 patients were men, their ages ranged from 17 to 69 years (average 53 years) The leading symptoms were intermittent claudication (176) and rest pain (26) without necrotic complications All patients were operated on with epidural anaesthesia

At the time of the procedure three or four small skin incisions were performed on the anterio-medial aspect of the tibia Then, three to five osteotomy perforations were carried out to produce small holes in the bone After the procedure is completed, skin sutures were placed without wound drainage. Haematoma formation with following aseptic inflammation resulted in revascularization of the affected limb During the 8 years of follow-up period good results were seen in 184 patients Forefoot or below-knee amputations were mandatory in 18 patients because of development of necrotic complications There was no mortality in our series.

Having performed stimulated osteotomy with acceptable perioperative morbidity, the operation was seen to provide good long-term results for treatment of LEOD

Pharmacological control of intimal hyperplasia

J. Kutlay*, E. Erdem†, C Ozaslan‡ and M Tunc§ **SSK Ankara Hospital, †Pamukkale University Medical School, ‡Ankara Oncology Hospital, §Akdeniz University Medical School, Turkey*

Intimal hyperplasia is the response to vascular trauma and leading cause of graft occlusion during the postoperative intermediate phase. Several pharmacological agents have been studied in the reduction of intimal hyperplasia In this study four groups of each containing 10 dogs were held and except the control group, three treatment groups received 1 mg/day silazapril (ACE inhibitor), 2·5 mg/day felodipine (calcium, channel blocker), and 100 AXA/kg nadroparine calcium (low molecular weight heparin), respectively for 4 weeks beginning on the morning of the operation In all animals a 2-cm length right common carotid artery was excised and a 2-cm length ipsilateral jugular vein was reversed and placed as end-to-end interposition vein graft into the common carotid artery. Four weeks later, animals were reoperated and grafts were harvested unblock after irrigation with 10 per cent formaldehyde solution Histological and morphometric analysis of intimal hyperplasia were evaluated. Intimal and medial thickenings and intima/media ratios were calculated Mean intimal thickenings were measured as 504 µm, 259 µm, 185 µm, 246 µm for the control, silazapril, felodipine, and nadroparine groups, respectively Mean medial thickenings were measured as 649 µm, 497 µm, 491 µm, 502 µm for the control, silazapril, felodipine, and nadroparine groups, respectively. Mean intima/media ratios were calculated as 0·77, 0·51, 0 37, 0·47 for the control, silazapril, felodipine, and nadroparine groups, respectively In regard of intimal and medial thickenings, and intima/media ratio, there was a significant difference between the control group and the three treatment groups ($P < 0{\cdot}001$). Felodipine group had the least intimal thickening and intima/media ratio among the three treatment groups ($P < 0{\cdot}05$). However no significant difference was observed in medial thickening among the treatment groups ($P > 0{\cdot}05$) These results suggest that silazapril, felodipine, and nadroparine treatment have been significantly effective in control of the development of intimal hyperplasia

In situ venous valve construction

P. Labaš, J. Šimo, V. Štvrtinová and A. Okrucká
University Hospital Surgical Department, 813 69 Bratislava, Mickiewiczova 13, Slovakia

Deep-vein reflux is a major cause of calf pump failure and has been identified in up to 90 per cent of our patients with torpid venous ulceration Direct valve repair appears to be of limited value With seven patients with venous ulcers unresponsive to intensive conservative treatment we used valvuloplastic in the popliteal venous region based on vein wall intussusception first described by Wilson in 1991 in his experiment on dogs This technique is combined with autotransplantation of the valve in the segment of axillary vein used to prolong the popliteal vein All valves were patent immediately after construction and Harvey's test showed them to be competent Ulcers healed rapidly. All valves were checked 6 months after operation with descending phlebography and double scan and all were component.

Treatment of aortic aneurysm associated with gastrointestinal and biliary pathology

L Leone, L. Giacomelli, G. Pascarella, A. Schioppa, D. Cecchinelli and G. Battisti *III Surgical Department, University of Rome 'La Sapienza', V. Regina Elena 324, 00165 Rome, Italy*

The surgical treatment of abdominal aorta vascular lesions at present is complicated by the increasing number of patients with simultaneous pathologies of the gastrointestinal and biliary tract The international literature shows that the under-diaphragmatic vascular lesions are associated with cholelithiasis in 4·9–7 per cent of cases, with colorectal pathology (mostly cancer and inflammatory processes) in 8–15 per cent of cases, with gastrointestinal malignant tumours in 4–8 per cent of cases. The surgeon has hence to face the problem of performing one- or two-stage operations. A one-stage procedure may be complicated by contamination of the vascular graft whereas a two-stage procedure brings the risk of an aneurysmatic disruption of gallbladder inflammation or intestinal obstruction The purpose of this paper is to demonstrate, on the basis of personal experience (289 patients from May 1989 to December 1995) the best route to be followed in view of a prosthetic infection, morbility and mortality reduction

The role of malignancy and preoperative embolization in the management of carotid body tumours

C. Liapis, A. Gougoulakis, E. Evangelidakis, B. Karydakis, V. Papavasiliou, C. Verikokos, P. Dousaitou, J. Gogas and M. Sechas *2nd Department of Propeudeutic Surgery, 3rd Department of Surgery, Athens University Medical School, Laiko General Hospital, Athens, Greece*

The purpose of this study is to describe our approach to the management of patients with carotid body tumours (CBT), emphasizing malignancy and preoperative embolization.

Between 1975 and 1996, 18 patients with CBT were treated in our department. There were seven men and 11 women with a mean age of 45 years (24–72 years). Six of the tumours (33·3 per cent) were type I, six (33·3 per cent) type II and six (33·3 per cent) type III according to the Shamblin classification. In 16 cases there was a successful excision of the tumour, while in three (two of type II and one of type III), preoperative embolization had been performed. The mean intraoperative blood loss was 700 ml in the 13 cases without preoperative embolization and 400 ml in the three cases with preoperative embolization. Two patients with tumours intracranially underwent only radiotherapy Neither postoperative deaths nor cerebrovascular complications occurred. Temporary cranial nerve injury occurred in four cases (two of the hypoglossal nerve, one of the glossopharyngeal nerve and one of the mandibular branch of the facial nerve). The pathology reports were paragangliomas in all cases. In two cases the tumours were considered to be malignant because of the local lymph node invasion. In these two cases no adjuvant therapy was required. Follow-up of the patients (from 6 months to 21 years) consisted of ultrasound for all cases and CT scan for the two cases with malignant tumours and revealed no recurrence in the 16 patients in whom surgical excision was performed, while in the two patients who underwent radiotherapy there was local recurrence. Surgical excision is the treatment of choice for the CBT, regardless of the malignant or benign behaviour of the tumour cells. Preoperative embolization contributes in the reduction of intraoperative blood loss.

Peripheral aneurysms of lower limbs

G. Mariani*, M. Andreoli*, R. Miglioranzi†, C. Bosi* and R. Buzzacchi* **Division of General Surgery, †Anaesthesia Service, Ospedale di Ostiglia, Italy*

Aneurysms of the peripheral arteries are very rare, and more frequently involve popliteal or femoral tract, even if they are not as common as abdominal aortic aneurysms. These lesions often remain asymptomatic, because the popliteal region is an uncommon area of semiotic research, until the appearance of heavy claudication or, even worse, the event of acute thromboembolic occlusion.

Between September and November 1995 we saw four peripheral vascular aneurysms, two popliteal and two femoral. There were three males and one female with mean age of 77 years (range 61–86 years). In our patients the aneurysms were never found bilaterally. In two symptom-free patients (50 per cent) discovery was causal, in one (25 per cent) a sonography study of popliteal fossa was performed; in one (25 per cent) with acute ischaemia the treatment was intra-arterial fibrinolytic infusion followed by aneurysm resection. The mean aneurysm size was 7 cm (range 4–12 cm). Treatment consisted of total resection and anatomical reconstruction by means of saphenous vein interposition in one case and allograft in two

Popliteal aneurysms is a rather infrequent lesion which may cause severe ischaemia and loss of the extremity. The risk of developing thromboembolic complication was 25 per cent at 1 year rising to 70 per cent at 5 years. Therefore, even if asymptomatic or small, this is a potentially dangerous lesion that justifies elective surgery.

Ambulatory eradication of varices: results of the Carsena method

J.-L. Masson *3 rue d'Angleterre, 06000 Nice, France*

The 'Carsena method' or reticular and saphenous ambulatory surgery was developed, by a new therapeutic association in 1988 and is essentially based on three techniques used in synergy. (a) The ambulatory phlebectomy according to Muller; (b) The crossectomy + ambulatory short stripping of the saphenous vein with the help of the 'Azur strip', (c) The photocoagulation laser associated with the microphlebolysis. The study of more than 5000 associated operations, in 4 years on 1000 patients shows excellent short-, medium- and long-term results in all cases, after a 4-year period. These results are also obtained for peripheral functions affected by the surgery Our object is to preserve the patient's comfort during and after the operation and most of all to ensure a rate of aesthetic satisfaction higher by far than any other techniques used at present

Carotid thrombo-endarterectomy under cervical plexus block: our experiences in 98 cases

R. Miglioranzi*, G. Mariani†, M. Andreoli† and R. Buzzacchi† **Anaesthesia Service, †Division of General Surgery, Ospedale di Ostiglia, Italy*

We report on a retrospective review of our experience on 91 patients undergoing carotid thrombo-endarterectomy (TEAC) under regional anaesthesia (cervical plexus block). The main anaesthesiological problem in TEAC is the need to evaluate the neurological effects after carotid artery clamping during operation; in front of general anaesthesia, loco-regional anaesthesia permits a close neurological monitoring that is inexpensive, simple and reliable Another important advantage of this procedure is that the intraoperative shunt may be inserted only if necessary. From 1 January 1993 to 31 December 1995 in 91 patients we performed 98 cervical plexus blocks using the technique proposed by Moore As local anaesthetics we used mepivacaine 2 per cent or bupivacaine 0·5 per cent (max dose 30 ml). After 20 min the effect of the block was checked by the pinprick test; in seven patients, anaesthesia was judged insufficient and general anaesthesia was performed. During operation the patients were premedicated with atropine plus benzodiazepine (5–10 mg) or dehydrobenzperidol (1–2 ml), and, if necessary, with additional infiltration of mepivacaine 2 per cent provided by the surgeon In the 98 blocks we observed the following complications: laryngeal nerve block with dysphonia (5), Bernard-Horner syndrome. (3), intra-operative vomiting (3), phrenic nerve block (one case the operation was delayed); no other major complications.

The technique has proved to be of easy execution, with low risk of complication, safe also for high-risk patients, and well accepted by the patient and the surgeon.

Local sympatectomy in chronic vasospastic syndromes of the hand

A. Ortensi*, F. Curini Galletti†, V. Marchese*, F. Stocco* and A. Lentini* **Servizio di Microchirurgia, Istituto di III Clinica Chirurgica, Università di Roma 'La Sapienza', †Ospedale della Misericordia Grosseto, Divisione di Ortopedia, Rome, Italy*

The present study aims to underline the great support provided by microsurgical technique in solution of ischaemic phenomena of upper extremities. In particular those situations such as arteriolar vasospasm in Reynaud's disease, unsuccessfully treated with medical therapy, are considered.

Reynaud's disease frequently accompanies collagenopathies in which vasculitis is caused by autoantibody reaction The stereotypic patient is a young female at premenopausal age in whom vasospastic syndromes cause the early appearance of digital ulcers and then the partial or the entire necrosis of a digital segment. the result is disability as well as the simple unaesthetic appearance.

Microsurgical technique proposed consists in the ablation of the vasospasm with the aventectomy of digital arteries injured by the ischaemic process Therefore vasoconstrictive sympathetic adrenal terminations are interrupted. The study has been performed on 10 female patients (<37–54> years of age) with clinical history of systemic disease for 4 years and poor control of digital ischaemic symptoms (intense pain, intolerance to cold, nail distrophy, partial or total necrosis of a distal phalanx) Thermal stress test resulted negative for vasospasm in all of the cases Even though results are still preliminary, it is very important to stress the validity of such a technique on patients who do not have any improvements from medical therapy We do not have long-term results; but recent literature (Koman 1994, Ward 1994, O'Brian 1992, Jones 1991) supports our good results after 2 or 3 years post-surgery.

The return of the symptoms after 5 years, as suggested by some authors, allows a better quality of life in the expectance of future findings and solutions

Use of venous angioscopy for treatment of saphenous vein insufficiency

G Quarto, M. Santoro, G. Raimondi, G. Cerracchio and P. Forestieri *Department of General Surgery, Faculty of Medicine, 'Federico II' University, Naples, Italy*

Introduction: Recently, the vascular angioscopy assumed an important role both for its diagnostic and for its therapeutic applications In the former case, it makes possible the study of valvular structure, the identification and localization of valvular and parietal alteration, the localization of perforating veins, the individualization of a venous thrombus In the latter, it allows the performance of venous thromboembolectomy, infusion of fibrinolytic drugs for local thrombolysis, endoscopic sclerosis of varicose veins and incontinent perforating veins, endoscopic valvuloplasty calibraiton

Materials and methods: From 1993 up to now, 20 patients afflicted by varices of the long saphenous vein area have been observed in our department. We utilized an Omega OM 4/220 Angioscope with the following characteristics four functions, external diameter 2·28 mm, length 900 mm, work channel 0·70 mm, angulation 70°, 6000 pixel, with a peristaltic pump for blood washing.

Results and conclusions: The endoscopic exploration was carried out up to saphenous/femoral junction in all patients with a median time of 22·5 min (range 20–30 min). We obtained a confirmation of pre-operating duplex Doppler sonography results. In fact, the ostial valve appeared intensely altered with prolapse or absence of valvular border in all cases Moreover, with regard to Doppler c w and duplex Doppler sonography, a better internal individualization and cutaneous localization of incontinent perforating veins has been observed. All the operations were performed in spinal anaesthesia and in one-day surgery

A technique for prevention of saphenous nerve injury caused by stripping of the long saphenous veins

P. Sorrentino, U. Baccaglini, C. Castoro, G. Spreafico, P. Pavei, R. Polo, C. Famiglietti and E. Ancona *2nd Department of General Surgery, Ospedale Busonera, Via Gattamelata, 64, 36128 Padova, Italy*

The purpose of this study was to prevent sensory impairment in the cutaneous distribution of the saphenous nerve (SN) caused by stripping of the long saphenous vein (LSV). The study was a prospective one of a consecutive series of patients

Seventy-five patients were enrolled with primary LSV varices and reflux from the sapheno-femoral junction (SFJ) to the ankle, documented by duplex Seven patients were excluded· five for the presence of trophic cutaneous lesions due to chronic venous insufficiency and two for previous sclerotherapy treatments below the knee. Sixty-eight patients underwent high ligation and stripping of the LSV from groin to ankle, under monolateral subarachnoidal anaesthesia on day surgery.

For the surgical technique, after high ligation of the SFJ, an internal modified metallic stripper was inserted from groin to ankle where a short incision anteriorly and below the internal malleolus was performed An external modified Mayo stripper used to dissect the vein and to section collateral branches from groin to upper calf, and then an upwards invagination of the vein from ankle to upper calf completed the stripping. Adhesive short stretching bandage was applied immediately after the operation and patients were allowed to walk Intra-operative and post-operative complications were recorded All patients were evaluated for subjective and objective sensory impairment in the cutaneous distribution of the SN, 1, 3 and 6 months after the operation. No intra-operative complication was recorded. Stripping of the LSV was complete in all cases without any rupture of the veins and no postoperative haematoma. One out of 68 (1·5 per cent) evaluable patients had an area of 16 cm^2 of hypoaesthesia persisting at 12 months' follow-up

Incidence of paraesthesia varies widely in published series Best results have been reported with the invagination technique by Van Der Strichts, but this technique is associated with a high incidence of vein rupture and incomplete stripping. Our approach combining external and invaginated stripping resulted in a very low complication rate without any rupture of the vein

Surgical treatment of revascularization of aorto-iliac obstructive arteriopathy: a technical variant

A. Thau *Surgery Department, Service of Vascular Surgery, CTO Hospital, Azienda USL, Rome, Italy*

The author proposes a variant in the traditional surgical technique for treatment of obstructive aorto-iliac arteriopathy, to reduce the iatrogenous damages to sexual function. The surgical technique is summarized in three points· (a) short opening of the retroperitoneum, (b) use of vascular stapler, (c) end-to-end anastomosis of prosthesis-aorta

Out of a total of 240 aortic grafts performed in the last 10 years, 70 patients were treated for aorto-iliac obstructive disease. In the last 36 cases we adopted the suggested technique Fifty-nine patients are alive at follow-up We treated 23 patients with traditional technique and 37 with the suggested method. Three patients of the first group and only one of the second have failed to achieve ejaculation or have had retrograde ejaculation postoperatively

Prophylactic and therapeutic use of defibrotide in mesenteric ischaemia

G. Yetkin, M. Uludağ, A Çakmak, A. Işgor, D Doğusoy and O. Ulutin *Şişli Etfal Hospital, İstanbul, Turkey*

Defibrotid has strong antithrombotic effect, however it has no anti-coagulation effect. Its ischaemia and infarct-zone reducing effect had been shown with different parameters (by many investigators) in experimental studies

In our study, the effect of intramuscular therapeutic and prophylactic use on experimental superior mesenteric arterial thrombus was examined For this purpose we used 21 Wistar–Albino type rats. Three groups composed of 21 rats were studied. In all study subjects thrombus was formed by SMA occlusion for 30 min After this point occlusion was removed and reperfusion was obtained. To the first group (control group) serum physiological and to the second group (therapeutic defibrotid group) 20 mg/kg defibrotid was injected intramuscularly. This dosage was repeated 12 h later. In the third group (the group of prophylactic defibrotid) defibrotid was administered 20 mg/kg/dose intramuscularly 24 h and 12 h before operation Some amount of defibrotid was repeated at 12 h and 24 h after operation. For statistical analysis Mann–Whitney *U*-test was used. All rats were killed at 24 h after operation and in the occluded zone the small intestine segments with mesentry were removed and examined histopathologically The score of intestinal ischaemia was found to be low in the therapeutic and prophylactic groups compared to the control group. There was no statistically significant difference between the control group and therapeutic defibrotid group ($P > 0{\cdot}05$) whereas the difference between control group and prophylactic defibrotid group was significant ($P < 0{\cdot}01$).

These results show that defibrotid usage will be useful in the prophylaxis of mesenteric ischaemia

Simultaneous vascular and alimentary tract reconstruction: another concept for graft-enteric fistula treatment

K. Ziaja, M. Zaniewski, E. Majewski, M. Kazibudzki, M. Długaj, T. Urbanek, J. Samorodny and A. Krupowies
Department of General and Vascular Surgery, Silesian Medical School, 40-635 Katowice ul. Ziołowa 45, Poland

Fistula between the vascular prosthesis and the duodenum or the intestinal loop is observed in 0·2–4 per cent of patients previously operated on for aorto-iliac occlusions The complication is extremely dangerous and difficult to treat

Methods: Fifteen patients were operated on for a graft-enteric fistula. The following types of fistulas have been observed: (a) fistula between the 'trunk' of the prosthesis and the duodenum with little or without inflammation in the surrounding tissues; (b) fistula between the site of aorto-prosthetic anastomosis and the duodenum with marked inflammation, (c) fistula embracing the site of aorto-prosthetic anastomosis, the 'trunk' and limbs of the prosthesis with frequent periprosthetic or retroperitoneal abscess. In all our patients we performed vascular and alimentary tract reconstruction simultaneously

Results: The vascular reconstruction comprised (a) axillo-(bi)femoral bypass and ligation of the aorta; (b) *in situ* replacement of the prosthesis, (c) aorto-femoral bypass from the level of the diaphragm. The alimentary tract repair comprised (a) resection of the duodenum and Roux-en-Y jejunoduodenal anastomosis, (b) duodenal defect was sutured. There were four deaths. Acute respiratory insufficiency was commonly observed No intestinal or vascular complications were observed in any surviving patient.

Conclusions: The method of vascular and alimentary tract reconstruction is determined by the above-mentioned type of fistula

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1997 SUBSCRIPTION INFORMATION
The British Journal of Surgery (ISSN 0007-1323) is published monthly. All subscriptions are entered on a calendar-year basis, beginning in January and expiring the following December. Back issues are available, please contact us for details.
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01-04-97
P-173
A6(2)

18/2/97

Volume 83 Number 12 December 1996

The British Journal of
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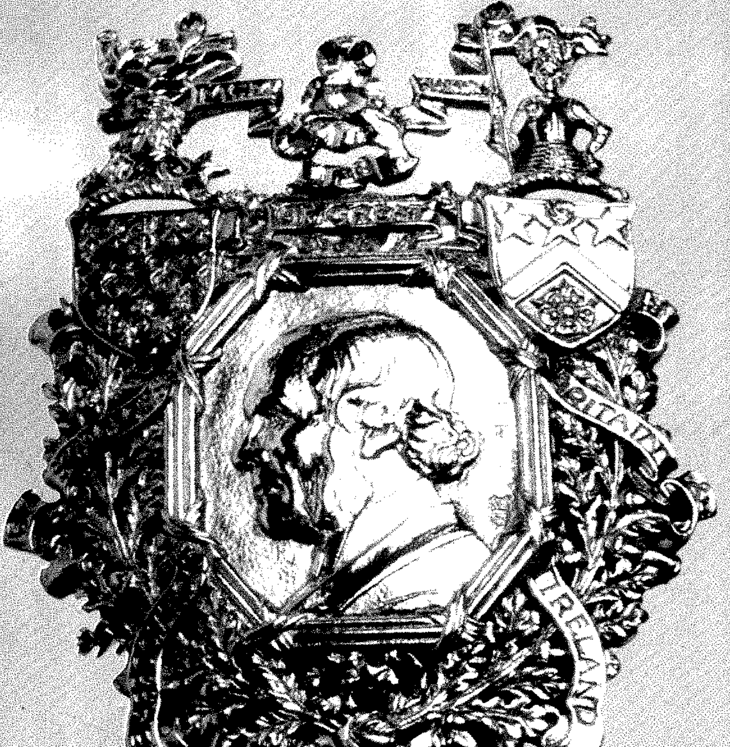

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ISSN 0007-1323

Typeset by Unicus Graphics Ltd
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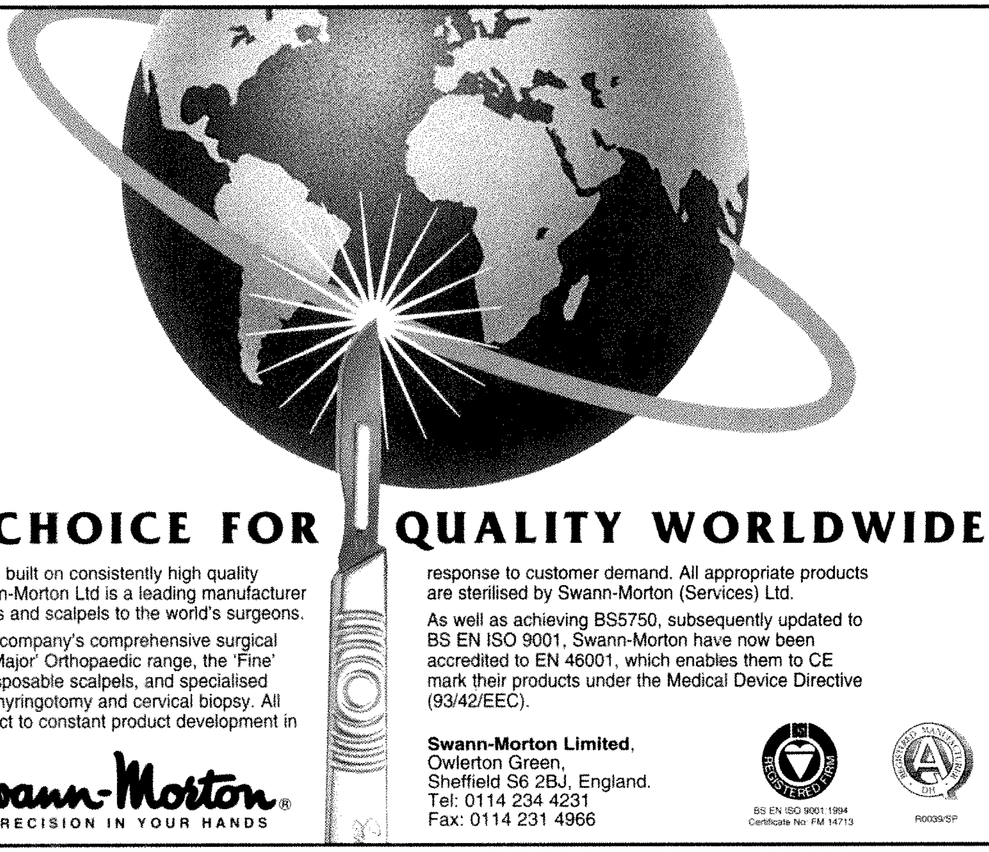

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Candidates for these scholarships should apply for an application form to the Secretary of the AESGBI - (Mr D C Dunn, Box 210A, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ) enclosing a copy of their C.V. and a brief resume of what they hope to achieve from this opportunity by **14th February 1997**. Names of successful applicants will be announced at the Association of Surgeons meeting in Bournemouth in April, 1997.

British Journal of Surgery 1996, **83**, 1665–1667

Leading articles

Somatostatin in pancreatic disease

A single agent that treats acute and chronic pancreatitis, controls pancreatic fistula, reduces operative morbidity and mortality rates, and even helps in the management of some pancreatic tumours would seem to be the alchemist's dream. Is somatostatin the fulfilment of this dream for the pancreatic surgeon? The answer is not easy, except to say that the therapy does not produce dramatic results and, despite many trials (often of low validity), definitive statements cannot be made about the use of somatostatin in clinical practice. Somatostatin is a cyclic peptide consisting of 14 amino acids and is best regarded as a phylogenetically ancient multigene family of peptides with two important bioactive products: somatostatin 14 and somatostatin 28. It modulates neurotransmission in the central nervous system and regulates the secretion of growth hormone and thyrotropin. It has a regulatory role in the gastrointestinal tract, as well as in the exocrine and endocrine pancreas. When synthesized and released by endocrine and nerve cells in the gastrointestinal tract and pancreas, somatostatin acts in an autocrine, paracrine or neuronal regulatory manner to inhibit glandular secretion, neurotransmission, smooth muscle contractility and absorption of nutrients. It also inhibits the function of activated immune cells[1].

It is hardly surprising that a transmitter with such wide-ranging actions has more than a single specific effect on the pancreas of use to the pancreatic surgeon. There are four properties of somatostatin that may influence the course of pancreatic disease: (1) inhibition of pancreatic secretion; (2) haemodynamic effect, reducing pancreatic blood flow; (3) cytoprotection; and (4) stimulation of the reticuloendothelial system[2]. Clinical use of somatostatin was initially hampered by its short duration of action and postinfusion rebound hypersecretion of hormones. Octreotide, the first somatostatin analogue introduced for clinical purposes, has a longer half-life and so is of practical use in the management of pancreatic disease.

One of the most effective uses of octreotide is probably in the management of pancreatic islet cell tumours. Some 7 per cent of all pancreatic tumours are of neuroendocrine origin. Most are non-secretory and do not express somatostatin receptors; nevertheless some do, are slowly growing and often secrete substances that cause considerable clinical disturbance, depending on the dominant hormone produced. Clinical improvement occurs in 50–85 per cent of affected patients during treatment with octreotide 150–800 μg per day, given as a subcuticular injection at intervals of 8 h. Patients learn to inject themselves and often are able to regulate their dosage according to the degree of symptom control. Such therapy may be combined with a proton pump inhibitor if there is excess secretion of gastrointestinal fluid. These patients are often neglected and mistreated as having inoperable pancreatic cancer for which there is no palliation; their good response can be gratifying.

The second indication for octreotide relates to pancreatic surgery. There are now four clinical trials suggesting that octreotide can substantially reduce the risk of complications after surgery for both benign and malignant disease, but none is conclusive because the current low mortality rate from pancreatic operations has meant that the studies have had insufficient power to show a decrease in mortality overall[3,4]. Nevertheless, the reduction in complications and length of stay suggest that after operation subcutaneous octreotide 100–200 μg at intervals of 8 h for 5–7 days is an appropriate adjunct.

The third indication is in the management of pancreatic fistula. Patients treated with a regimen of nil by mouth, total parenteral nutrition plus somatostatin had fistulas close within a significantly shorter time, with a reduction in the length of hospital stay[5]. Some studies, however, are confused by the type of underlying fistula. It is pointless administering octreotide to patients whose fistula arises from the body or tail of the pancreas, separated from the head of the gland, or to those who have a stricture in the head of the pancreas, unless the stricture is relieved, for instance by a stent. The ideal patient is fit and has an intact main duct with a side-branch fistula after an attack of acute pancreatitis. Subcutaneous octreotide 50–200 μg three times daily is used according to response. An interesting side-effect of this regimen is that, although the volume of pancreatic juice decreases, the enzyme concentration may rise progressively. Thus, if complications occur, appropriate surgical action is indicated.

The fourth indication is in a patient who has sustained trauma; this is not proven but, in view of the high incidence of fistula formation, would seem efficacious provided the pancreatic trauma is localized and the chance of fistula formation is high. Octreotide is not indicated for prophylaxis in patients having endoscopic pancreatography or sphincterotomy; extensive studies have failed to show benefit from routine prophylactic octreotide administration[6]. The explanation for this may be the complex effect of somatostatin on the sphincter of Oddi, which may impair biliary and pancreatic flow.

A fifth, but rare, use of octreotide is in pancreatic transplantation. A single study has suggested that the reduction in the output of pancreatic juice may be beneficial and, used selectively, octreotide can result in graft salvage with lowered morbidity[7].

Perhaps the area of greatest debate relates to pancreatitis. In chronic pancreatitis there is no support for the use of octreotide in the management of pain or complications, apart from fistula. It does not aid the management of pseudocysts, but is useful for pancreatic ascites, which may be considered an incomplete fistula. While there is no evidence to support the routine use of octreotide in the general long-term management of chronic pancreatitis[8], no such didactic statement can be made for acute pancreatitis. After an attack of acute pancreatitis the secretory capacity of the pancreas is impaired to a degree related to the severity of the inflammatory process. The pathophysiological prerequisites for the use of secretion inhibitor substances in acute pancreatitis have not been established. In controlled trials, although octreotide failed to produce a statistically significant improvement in mortality, it was associated with lower complication rates. In a meta-analysis, Carballo *et al.*[9] considered six studies and concluded that somatostatin significantly reduces the mortality rate associated with acute pancreatitis. Nevertheless, evidence from experimental studies remains inconclusive and in the clinical setting only a very small proportion of patients is likely to benefit, suggesting that any controlled trial in the future will have to be very large to reveal this small advantage. On an empirical basis it is reasonable to give subcutaneous somatostatin 100–200 μg three times daily to patients with severe acute pancreatitis during the first 14 days of illness, in line with the favourable outcome suggested by the most recently published study[10].

As in so many spheres, the balance of cost (octreotide is an expensive drug) and benefit is important. Evidence-based surgery fails to provide clear guidance, as is so often the case; the enlightened surgeon will limit the use of octreotide to selected patients for defined periods, ensuring that, while no patient is disadvantaged, the cost is contained.

R. C. G. Russell

Department of Surgery
The Middlesex Hospital
London W1N 8AA
UK

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Editors' announcement

Structured abstracts

The Journal has watched with interest developments in the presentation of abstracts in scientific journals. We have seen some journals adopt abstracts with 12 or more subheadings, each supported by a few words. In the defence of good readable prose, we resisted moves towards that style. However, we are aware that breaking up an abstract into several paragraphs may improve its readability and enable the reader to grasp the content more effectively. Four paragraphs suffice, corresponding to the introduction, methods, results and discussion sections of the paper in order to accommodate this extra information. The Editors recognize that a larger word limit than the present 150 words will be necessary.

With effect from the January 1997 issue, all abstracts will be printed in the following format: they will be no more than 200 words long, written in clear prose, and presented in four paragraphs.

Background. This should state why the study was done and its main aim.

Method. This should describe the patients, laboratory material and other methods used.

Results. The main findings of the study should be stated briefly, including important numerical values.

Conclusion. The main conclusion drawn from the results should be stated. Controversial or unexpected observations may be highlighted but this section should be brief.

Authors whose papers have already been accepted and are scheduled for publication in 1997 will be asked to revise the abstract in accordance with these guidelines. Instructions for Authors have been revised and all new submissions to the Journal should take account of these revised instructions. Please note that only original articles and reviews require an abstract.

R. C. N. Williamson
J. A. Murie
C. D. Johnson
J. J. Earnshaw
P. J. Guillou

British Journal of Surgery 1996, 83, 1668–1669

Gut barrier function in the surgical patient

A failure of the gut barrier to exclude endogenous bacteria and toxins from mesenteric lymph nodes and the portal and systemic circulation is incriminated in the systemic inflammatory response syndrome, sepsis and multiple organ failure[1]. Consensus is emerging that the barrier function of the gut is relevant in established critical illness and in patients at risk of developing sepsis as a result of either an immunoinflammatory insult, such as burns, trauma, shock and severe pancreatitis, or preoperative debility, including severe malnutrition, jaundice and immunosuppression. Although this concept has logical appeal and is supported by compelling animal data, it is timely to review the corroboration available from clinical research.

Direct corroborative studies have focused on the search for bacterial and endotoxin translocation. In animal models this occurs in immunoinflammatory states, immunosuppression, shock, gut ischaemia and gut starvation. Most studies in humans have focused on multiple trauma and, as recently debated in this Journal, consistently indicate that bacterial translocation is rare and does not correlate with outcome; portal and systemic cultures are, by and large, sterile[2]. A number of investigators have cultured mesenteric lymph nodes and serosa at laparotomy. In the largest study Sedman *et al.*[3] reported that colonization is extremely rare, occurring in approximately 10 per cent of 267 patients, and was more common in those with distal bowel obstruction and inflammatory bowel disease. In small subsets of patients with jaundice or malnutrition, or in those who had received preoperative total parenteral nutrition, there was, in marked contrast to the animal models, no significant evidence of translocation.

Despite the lack of concordance between animal models and humans when bacterial translocation alone is sought, indirect clinical evidence appears to support the thesis. The gut has enhanced nutritional, metabolic and oxygen requirements in established immunoinflammatory states. An ability to tolerate high protein enteral nutrition is tightly associated with reduced septic morbidity and with improved outcome in patients with multiple trauma and in children with severe burns[4,5]. Prospective randomized studies and meta-analysis comparing early enteral nutrition and total parenteral nutrition suggest that the former reduces septic complications and suppresses the exaggerated cytokine and acute-phase responses associated with major trauma, surgery and pancreatitis[6,7].

How can this indirect evidence be reconciled with the real lack of direct supportive evidence? A possible explanation for the lack of direct support is that attempts to corroborate the animal model findings in humans have been too simplistic and literal. Bacterial translocation in the laboratory animal may simply be a marker of gut barrier failure, no more and no less. Thus the more logical question to pursue in humans may be: does gut barrier failure occur and what is its clinical significance? The gut barrier, in addition to its role in limiting bacterial and endotoxin translocation, also prevents the uptake of undegraded antigens and regulates the development of potentially harmful local and systemic immune responses. The intestine is the largest immune organ in the body and the complex gut-associated lymphoid tissue contains approximately 40 per cent of the immune effector cells in the body. When it is considered that the intestine behaves as a unit functionally, anatomically and metabolically with the liver, the liver itself being a vast reservoir of immunological cells (particularly Kupffer cells), it is evident that activated leucocytes and proinflammatory cytokines within this splanchnic unit may influence regional and systemic immunoinflammatory responses. Although these responses may be triggered by bacterial or cell wall antigen, they may also occur in response to other antigens not yet defined, or in direct response to gut injury, hypoxia or ischaemia–reperfusion. Within this scheme enteral nutrition may act at several levels, including altering antigen exposure, modulating splanchnic immune responses, enhancing mucosal protection and, perhaps, influencing blood supply and oxygenation of the mucosa, as oxygen consumption may be markedly increased in immunoinflammatory conditions[8].

The integrity of the gut barrier in humans is most readily assessed by measuring gut permeability. Permeability is increased following trauma, surgery and burns, and in patients with jaundice, malnutrition and inflammatory bowel disease[9]. The dual-sugar or radiolabelled probes commonly used have been criticized because they reflect a paracellular phenomenon, whereas bacterial translocation appears to occur via a transcellular mechanism. Although valid, this criticism should not detract from the fact that gut barrier function is impaired compared with relevant controls. The overall objective of research in this area should be to determine whether this finding makes a difference to the patient. Specifically, does increased intestinal permeability in the high-risk surgical patient correlate with an increased risk of systemic inflammatory response syndrome and sepsis? If so, can this be reversed and does restoration of permeability to normal reduce the risk? Does increased permeability correlate with abnormal intestinal morphology, dysregulated local immune function or altered microbiological flora? Is altered gut barrier function associated with an altered systemic cytokine profile and an exaggerated acute-phase response, or with evidence of endotoxin exposure? Most intriguingly, and in keeping with the two-hit hypothesis of sepsis, is compromised gut barrier function associated with priming of gastrointestinal and systemic immune cells, such that further activation in response to surgical trauma or an infective challenge magnifies the autodestructive cytokine response resulting in systemic inflammatory response syndrome and sepsis[1]? Finally, does enteral nutrition truly modulate gut barrier function in humans or is tolerance of enteral nutrition *per se* a marker of a healthy organ system, and thus linked with better outcome and of greater significance than the apparent benefits of the nutrition itself?

We are nowhere near a full understanding of the relevance of gut barrier function in the surgical patient. Careful prospective study is needed. Intervention studies are required in established immunoinflammatory states, ranging from assessment of enteral nutrition and specific fuels, such as glutamine and growth factors, to splanchnic vasodilators; these will have much greater significance if baseline data can be established for each patient. Similarly, in patients at high risk of postoperative sepsis the baseline problem needs to be defined comprehensively if solutions based on unproven assumptions are not to be proffered.

J. V. Reynolds

Academic Surgical Unit
Clinical Sciences Building
St James's University Hospital
Leeds LS9 7TF
UK

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British Journal of Surgery 1996, **83**, 1670–1673

New Members of the Editorial Board

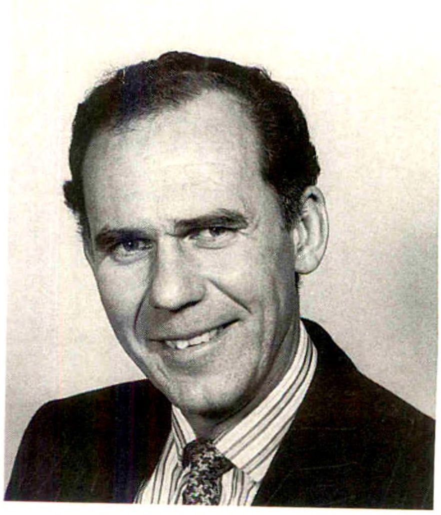
A number of surgeons from Britain and overseas have joined the Editorial Board of the Journal during 1996. We present a short synopsis of their biographical data and clinical interests.

MR RONAN O'CONNELL
(Ireland)

Patrick Ronan O'Connell (born 1956) was appointed as Consultant Surgeon at the Mater Misericordiae Hospital, Dublin in 1990. He graduated from Dublin University (Trinity College) in 1979 and trained at Dublin, Cork, London and the Mayo Clinic, Rochester, Minnesota, USA. A previous winner of the Patey Prize (Surgical Research Society), he is a Member of the European Council of Coloproctology. His particular interests are in anorectal physiology and inflammatory bowel disease.

MR BRUCE CAMPBELL
(Exeter)

William Bruce Campbell (born 1950) is Consultant in Vascular and General Surgery at the Royal Devon and Exeter Hospital, Exeter (since 1986). A Bart's graduate, he trained in Southampton, Bristol and Oxford. He won the Hallett Prize of the Royal College of Surgeons of England and was Hunterian Professor in 1983–84. He is an FRCP as well as an FRCS. He has numerous publications on the investigation and treatment of arterial and venous disease.

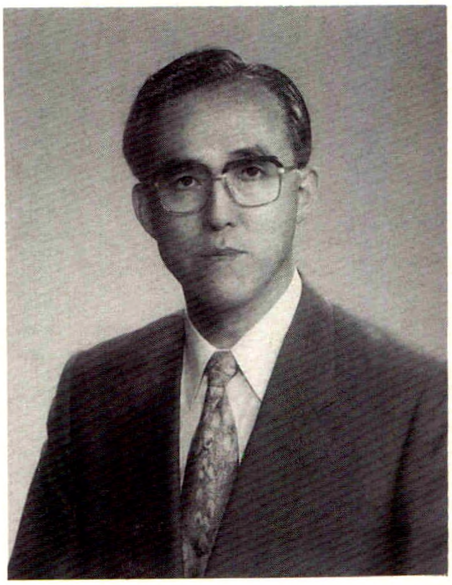


DR LAYTON RIKKERS
(USA)

Layton F Rikkers is AR Curreri Professor and Chairman of Surgery at the University of Wisconsin Medical School, Madison, USA. Graduating from Stanford University, he trained in Utah with fellowships in Atlanta and at the Royal Free Hospital, London before being appointed to the Chair of Surgery at Omaha, Nebraska (1984–1996). He is President-elect of the Society of Clinical Surgery and recent Chairman of the American Board of Surgery. His clinical and research interests lie in the field of HPB (hepatopancreatobiliary) and gastrointestinal surgery, especially the treatment of portal hypertension.

PROFESSOR KEIZO SUGIMACHI
(Japan)

Keizo Sugimachi (born 1938) is Professor and Chairman of the Department of Surgery at Kyushu University, Japan and Dean of the School of Medicine. He received all his training in Kyushu except for 1 year as Research Fellow at Hahneman University, USA. He is Editor of *Surgery Today* (*Japanese Journal of Surgery*), the *Japanese Journal of Hyperthermic Oncology* and *Hepato-Gastroenterology.* He is a prolific author of papers in both English and Japanese on a wide variety of surgical topics.



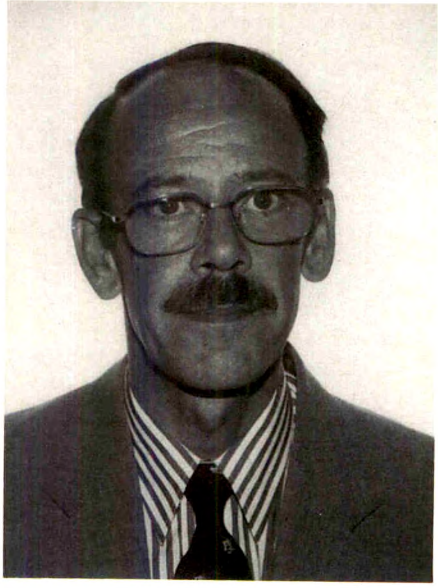
PROFESSOR MASAKI KITAJIMA
(Japan)

Masaki Kitajima, who was born in 1941, is Professor and Chairman of Surgery at Keio University, Japan and Vice-Director of Keio University Hospital. He trained at Keio and the Massachusetts General Hospital, Boston, USA. He became successively Assistant Professor, Associate Professor and Professor at Kyorin University, Japan before taking up his present post in 1991. He is on numerous editorial boards of journals dealing with endoscopic and gastrointestinal surgery and is a Director of the Japanese Surgical Society.

PROFESSOR FREDDY PENNINCKX

(Belgium)

Freddy Penninckx was born in 1947 and was appointed to the Chair of Surgery at the Catholic University, Leuven, Belgium in 1989. He obtained his PhD thesis for work on the structure and function of the anal sphincter while serving as a Lecturer in Surgery at Leuven in 1981. His interests embrace many different aspects of gastrointestinal surgery including colorectal cancer, peritonitis and intestinal ischaemia. He also serves on the Editorial Board of the *International Journal of Colorectal Disease.*



DR JOHN CORSON

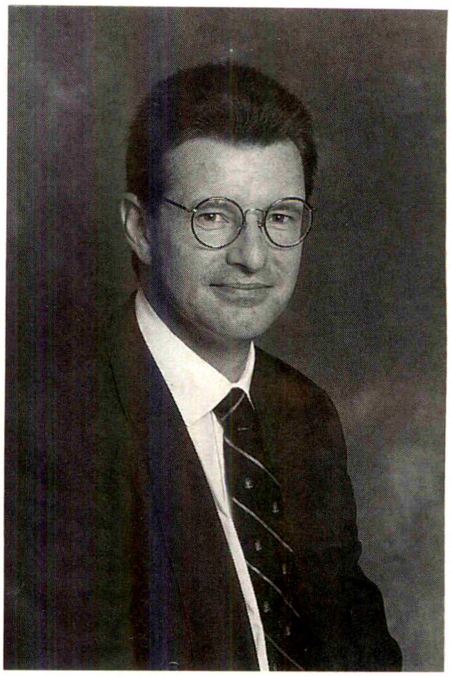
(USA)

John Duncan Corson was born in 1946, was educated in Scotland and graduated in 1968. He worked as a Surgical Registrar in South Wales before moving to Boston University in 1974, where he undertook a research fellowship and then the residency programme. He is currently Professor and Chief of Vascular Surgery at the University of Iowa, USA. Dr Corson has a particular interest in the use of vein bypass grafting for limb salvage. He is President of the Society for Clinical Vascular Surgery.

PROFESSOR JOHN MONSON

(Hull)

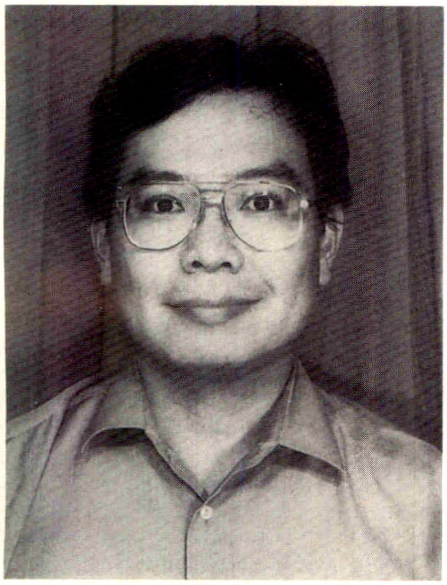
John Rowat Telford Monson (born 1956) is Foundation Professor of Surgery at Hull. He qualified from Trinity College, Dublin in 1979 and carried out his early surgical training in that city. Subsequently he worked at Leeds and the Mayo Clinic, USA and then became Consultant Senior Lecturer at St Mary's Hospital, London. Awarded his MD thesis in tumour immunology and cytokines, he has retained a strong interest in this area. He has a special interest in oncological and colorectal surgery and has published widely in the field of laparoscopic surgery.



MR KENNETH FEARON

(Edinburgh)

Kenneth Christopher Howard Fearon, who was born in 1960, is Reader in Surgery at the Royal Infirmary, Edinburgh. His surgical training took place in Glasgow and Edinburgh. His initial research was in medical oncology, but he subsequently trained in surgery with a particular interest in surgical oncology. His clinical interests are colorectal cancer and clinical nutrition, and his current research embraces cytokines, wasting and nutritional pharmacology.



MR FRANCIS SEOW-CHOEN

(Singapore)

Francis Seow-Choen is Head of the Department of Colorectal Surgery and Director of the Endoscopy Centre at Singapore General Hospital. He trained in Singapore but spent 1 year as a Clinical Assistant and Research Fellow at St Mark's Hospital, London before becoming a Consultant Surgeon in 1992. He has written extensively on many different aspects of colorectal surgery including haemorrhoids, anal fistula, rectal prolapse and pelvic pouch, and he runs a highly productive department. In addition he is a noted expert on phasmids (stick insects).

PROFESSOR FRANCISCO CASTRO SOUSA

(Portugal)

Francisco Jose Franquera de Castro e Sousa (born 1947) has been Chairman of Surgical Service III at Coimbra University Hospital, Portugal, since 1988 and Professor Catedrático of Surgery since 1990. He graduated from Coimbra in 1970 and trained largely in that city. He is President of the Directory Board of the Portuguese Society of Surgery and a member of the Editorial Board of fourteen medical journals. He is interested in all aspects of gastrointestinal surgery but especially HPB surgery.

Robin Williamson

British Journal of Surgery 1996, **83**, 1674–1683

Review

Papillary microcarcinoma of the thyroid gland

M. D. BRAMLEY and B. J. HARRISON

Department of Surgery, Northern General Hospital NHS Trust, Herries Road, Sheffield S5 7AU, UK
Correspondence to: Mr B. J. Harrison

Papillary microcarcinomas are a specific subgroup of papillary thyroid cancer. They have the same histological features as papillary thyroid cancer but are 1·0 cm or less in diameter. These tumours are a common incidental finding at autopsy and in thyroid glands excised for other pathology. This tumour can metastasize to regional lymph nodes but its ability to cause significant morbidity and mortality has been questioned. As papillary microcarcinomas can represent up to 30 per cent of all papillary cancers seen in a thyroid surgeon's practice, they are an important group. The aim of this review article is to outline the natural history of papillary microcarcinoma and to offer therapeutic management strategies.

Thyroid cancer is uncommon. It represents 1 per cent of all malignancies and was responsible for only 348 deaths in England and Wales in 1991[1]. It is still, however, the most common endocrine malignancy[2]. Papillary thyroid cancer is the most frequent histological subtype of thyroid cancer, accounting for 80 per cent of cases[3]. It may run an indolent course over many years and has a variable prognosis, irrespective of the presence of cervical lymph node metastasis[4,5]. Papillary thyroid cancer may be discovered incidentally during routine histological section of thyroid glands excised for other diseases[6] and small foci are also frequently found in autopsy specimens[7–24]. Prolonged follow-up of patients with papillary tumours of small size has shown that the prognosis is very good[6], but the management of incidentally discovered tumours is still unclear. The aim of this review article is to outline the natural history of papillary microcarcinoma and to offer therapeutic management strategies.

Historical perspective

The complex classification of thyroid cancer in the first part of the twentieth century was much simplified in 1925 by Graham[25] who described three groups, one of which was called papillary adenocarcinoma. These tumours were described as often cystic, less malignant and spreading to local lymph nodes. The term 'aberrant thyroid' was first suggested by Schrager[26] in 1906 and defined as 'a mass of tissue having the structure of a normal or pathologic thyroid, and situated as some *definite* distance from the normal thyroid, with which it has no connection whatever'. He concluded that these aberrant thyroids were benign and that the position of this tissue had an embryological explanation[27]. The term 'lateral aberrant thyroid' was coined to describe tissue that 'tended to occupy the same general location as the chain of deep cervical lymph nodes'[27]. It was soon shown that these tumours had malignant potential and should be 'studied with care, treated radically, and followed indefinitely'[27].

It was Wohl[28] in 1917 and later Eberts[29] in 1933 who contended that the so-called lateral aberrant thyroid tumours were, in fact, metastatic lesions from primary papillary adenocarcinomas of the thyroid. This was elegantly confirmed by Black[30] in a series from the Mayo Clinic, who reported on 112 patients in whom primary papillary adenocarcinoma was found on the same side of the thyroid gland as the corresponding lateral neck mass. The concept of lateral aberrant thyroid was therefore abolished and the term 'occult carcinoma of the thyroid'[31] introduced to refer to the appearance of metastatic thyroid tumour in the cervical lymph nodes of patients with no palpable thyroid abnormality.

An arbitrary diameter of 1·5 cm or less was chosen for the tumour focus[6]. The advent of improved preoperative diagnostic techniques, in particular fine-needle aspiration cytology (FNAC), has meant that small thyroid tumours can be diagnosed before definitive surgery[32] and hence are not clinically occult. The term 'papillary microcarcinoma' of the thyroid gland has therefore replaced the term 'occult' to describe these lesions. Papillary microcarcinoma (PMC) is defined according to the World Health Organization (WHO) as a tumour focus of 1·0 cm or less in diameter[33]. The analysis of previous studies for this review is difficult because of the variety of terms used to describe small thyroid carcinomas. For papers written before the WHO definition was coined, which include tumours greater than 1·0 cm in diameter but less than 1·5 cm, the term small papillary thyroid carcinoma (SPTC) is used in this review. Examination of SPTC is included here because it is not clear whether there is any biological difference between tumours 1·0 cm in diameter (PMC) and those of 1·5 cm or less (SPTC).

Pathology of papillary microcarcinoma

Papillary thyroid cancer is defined as a malignant epithelial tumour showing evidence of follicular cell differentiation, typically with papillary and follicular structures as well as characteristic nuclear changes (ground glass, large size, pale, irregular outline with deep grooves, and pseudoinclusions)[33]. The morphological spectrum of papillary thyroid carcinoma is broad and many variants have been described, including follicular, solid, cribriform, encapsulated, diffuse sclerosing, diffuse follicular, tall cell, columnar, oxyphil and undifferentiated[34]. Papillary thyroid carcinoma is typically invasive but can be circumscribed or encapsulated[34].

Paper accepted 21 August 1996

Calcified structures, psammoma bodies, are found in the stroma in approximately 50 per cent of cases[34].

PMCs are generally well differentiated. They exhibit characteristic cytological features of papillary lesions, namely ground glass nuclei, overlapping nuclear arrangements, nuclear grooves and occasional cytoplasmic invaginations into the nucleus[34]. In recent years a further subdivision of PMC has been proposed[35]. The terms 'tiny', referring to 5–10-mm diameter foci, and 'minute' for foci of 5-mm diameter or less were suggested because of differences in the incidence of lymph node metastasis (59 *versus* 13 per cent respectively) and extrathyroidal extension (10 *versus* 3 per cent)[35]. These terms have not been adopted in this paper because most of the information under review does not contain such a division.

Prevalence rates of papillary microcarcinoma

Autopsy studies

Autopsy reports from the 1960s onwards have revealed that small foci of papillary cancer are commonly found in the thyroid glands of individuals dying from unrelated illnesses, but comparison of the results of these autopsy studies[7–24] is difficult because of diversity in the definition, the pathological sectioning techniques used and the pathological criteria used to diagnose papillary thyroid cancer. In some[7–11,14–16,22], the focus of tumour is 1·5 cm or less in diameter; in others[12,13,17–21,23,24] the focus is 1·0 cm or less. Overall, the prevalence in autopsy material ranges from 1 to 35·6 per cent[7–24] (*Table 1*). Before any direct conclusions can be drawn, a closer look at the methods used to examine the material in each study is required. When foci of tumours of 1·0 mm or less in diameter are being identified, it is clear that sectioning the gland at 2–3-mm intervals will inevitably miss small lesions. This was elegantly demonstrated by the Spanish group[22], which divided autopsy material into two groups. Series A had sectioning of macroscopically abnormal areas plus one random section from each lobe, while series B had the entire gland sliced serially and transversely at 2–3-mm intervals. The prevalence of SPTC increased from 5·8 per cent in series A to 22·0 per cent in series B. Indeed the highest prevalence (from Finland) of 35·6 per cent was obtained by looking at the whole gland in 2–3-mm slices with 4-μm slices of each block, showing that 77 per cent of tumour foci were less than 1·0 mm in diameter[15]. In general in each autopsy study two experienced thyroid pathologists have each looked at all the material and diagnosed a papillary lesion only when both agreed. It is beyond the scope of this article to discuss the finer nuances of the diagnosis of papillary lesions, but it must be assumed that differences in opinion do exist between pathologists worldwide, for which no account can be made.

Table 1 Autopsy studies showing prevalence rates of small papillary thyroid carcinoma and papillary microcarcinoma of the thyroid gland

Reference	Country	Pathological method	Prevalence (%)
Small papillary thyroid carcinoma			
Sampson *et al* [7,8]	Japan		
	Hiroshima	a	18·1
	Nagasaki		17·3
Fukunaga and Yatani[11]	Japan	a	28·4
	Japanese living in Hawaii		24·2
	Canada		6·0
	Poland		9·1
	Colombia		5·6
Sampson *et al.*[10]	Minnesota, USA	a	5·7
Harach *et al* [15]	Finland	c	35·6
Martinez-Tello *et al* [22]	Spain	c	22·0
Papillary microcarcinoma			
Sobrinho-Simões *et al* [12]	Portugal	a	6·5
Bondeson and Ljungberg[13]	Sweden	b^1	8·0
Arellano and Ibarra[17]	Chile	a	3·6
Delides *et al.*[24]	Greece	e	1·5
Lang *et al* [18]	Germany	b^2	6·2
Ottino *et al* [19]	Argentina	c	11·0
Bisi *et al.*[20]	Brazil	d	1·0
Yamamoto *et al* [21]	Tokushima, Japan	a	11·3
Furmanchuk *et al* [23]	Belarus	e	8·8

Pathological methods key: a, 2–3-mm slices of macroscopically abnormal gland and one random slice from each lobe, b^1, 1–2-mm slices of macroscopically abnormal gland and one random slice from each lobe; b^2, 1–2-mm slices of macroscopically abnormal gland and one block per gram of normal thyroid gland, c, whole gland in 2-mm sections, d, 3-mm slices of macroscopically abnormal gland and one block per 5 g normal thyroid, e, 2–3-mm section of macroscopically abnormal gland and three to five areas at random from the thyroid gland

Geographical distribution (Table 1). Because the prevalence of PMC is so varied, other factors besides variation in pathological technique may account for the observed differences. Using identical sectioning techniques and pathologists, Fukunaga and Yatani[11] demonstrated a significantly higher prevalence of SPTC in Japan (28·4 per cent) than in Canada (6·0 per cent), Poland (9·1 per cent) and Colombia (5·6 per cent). Interestingly, the high prevalence was maintained in first- and second-generation Japanese living in Hawaii (24·2 per cent)[11], indicating the influence of environmental factors. High iodine intake is associated with a rise in the prevalence of papillary thyroid cancer[36], which may account for the increased prevalence of PMC in Japan[11] in contrast to low rates in the goitrous areas of Chile[17]. In a goitrous area of Argentina the addition of iodine to the water supply led to an increase in the prevalence of PMC[37]. The highest published rate of SPTC was found in Finland[15], in contrast it has the lowest incidence of clinically apparent thyroid carcinoma within Scandinavia. Indeed Harach *et al.*[15] concluded that the prevalence of SPTC was so high (35·6 per cent) that it should be considered a 'normal finding' and that the term carcinoma should not be applied to this lesion.

Sex differences (Table 2). In the majority of autopsy studies[8–11,13–24] no significant difference in the prevalence rate of PMC has been demonstrated between the sexes. Only reports from Portugal[12], and Hiroshima and Nagasaki in Japan[7] have shown a statistically significantly female preponderance. This is in sharp contrast to clinically apparent papillary thyroid carcinoma, which is more common in women[2].

Table 2 Autopsy studies showing the percentage of small papillary thyroid carcinoma in each sex

Country	Males (%)	Females (%)	Tumour size (cm)
Canada[11]	50	50	1·5
Sendai, Japan[11]	55	45	1·5
Poland[11]	20	80	1·5
Colombia[11]	68	32	1·5
Japanese in Hawaii[11]	48	52	1·5
Minnesota, USA[10]	78	22	1·5
Hiroshima and Nagasaki, Japan[7]	47	53	1·5
Portugal[12]	23	77	1·0
Sweden[13]	44	56	1·0
Chile[17]	40	60	1·0
Finland[15]	69	31	1·5
Germany[18]	38	62	1·0
Argentina[19]	73	27	1·0
Tokushima, Japan[21]	56·5	43·5	1·0
Brazil[20]	67	33	1·0
Spain[22]	73	27	1·5
Minsk, Belarus[23]	53·5	46·5	1·0
Greece[24]	33	67	1·0

Age distribution. Most autopsy studies have been performed in the 'over 40' population, with only limited data available in the old and in the younger age group. In Portugal the prevalence of PMC was significantly higher in an older age group (mean(s.d.) age 61·4(13·9) years)[12] but no other autopsy studies have demonstrated such an age-related difference. In younger age groups, two studies have shown no difference in SPTC prevalence rates between the 18–40-year-old group[14,16] and rates overall. Thus autopsy data suggest that PMC rarely progresses to clinically apparent thyroid cancer with advancing age.

Weight, multifocality and position of the tumour within the thyroid gland. In a Polish study, 32 per cent of the thyroid glands examined were enlarged but the prevalence rate of SPTC was only 9·1 per cent[11]. In an endemic goitrous area of Chile the rate of PMC was 3·6 per cent[17]. This indicates that there is no relationship between gland size and PMC. Tumour foci occur with the same frequency in both thyroid lobes and can occur in the isthmus[15]. Most tumours are located near the thyroid capsule: in a Finnish study, 45 of 50 tumours less than 5 mm in diameter were located within 2 mm of the thyroid capsule, and nine tumours involved the capsule[15]. Most autopsy studies[10,13,15,17–19,21–23] have demonstrated that PMC of the thyroid gland can be multifocal (*Table 3*). Each gland may contain from one to 17 foci of tumour in one or both lobes[17]. In the data from Finland[15] 36 thyroids revealed 52 foci of SPTC. Twenty-six glands contained one tumour, six glands contained two tumour foci, three glands three foci, and one gland five foci[15].

Frequency of cervical lymph node metastasis. In autopsy studies[7,13,18,19,21] where regional lymph nodes were available for scrutiny by the pathologists, the varying techniques of node sampling and preparation make direct comparisons between studies difficult. Cervical lymph node metastases from PMC have been shown in 4·3 per cent of cases in Japan[21], 18·2 per cent in Argentina[19], 3·1 per cent in Sweden[13] and 14·3 per cent in Germany[18]. In most cases the lymph node metastasis was on the same side as the thyroid focus, but nodes have been demonstrated bilaterally and even on the side opposite the primary focus[7]. Sampson *et al.*[7] concluded that lymph node metastasis was most often associated with multifocal tumours, and tumours with vascular and/or capsular invasion. In addition, the rate of lymph node metastasis was greater than 50 per cent if psammoma bodies were identified within the tumour[7].

Thyroidectomy specimens

Foci of PMC may be discovered when the thyroid gland has been excised for some other pathology. In only one study have results from autopsies and thyroidectomy specimens been compared together[24]. The prevalence of PMC was 1·5 per cent in the autopsy group, while in thyroidectomy specimens the rate of PMC was 1·8 per cent. Of the 11 PMCs from 611 resected thyroids, six were associated with multinodular goitre, three with toxic adenoma and two with Hashimoto's thyroiditis[24]. It was concluded that, because the autopsy prevalence rate was similar to the thyroidectomy specimen rate, the presence of PMC was not associated with other thyroid pathologies.

It was once thought that a diagnosis of thyrotoxicosis was a safeguard against thyroid cancer. Olen and Klink[38] dispelled this idea by demonstrating 53 thyroid cancers in 2114 thyroidectomy specimens excised from thyrotoxic individuals, 27 of these being foci of SPTC (1·3 per cent). Groups worldwide[39–44] have looked at the relationship of thyroid disease and SPTC (*Table 4*). The presence of coexisting thyrotoxicosis and PMC varies from 0·3 to 5·7 per cent in resected specimens (*Table 5*)[24,39–41,43–45]. Graves' disease has been associated with PMC in 0·6–5·7 per cent of cases[38–41,44,45]; in one study[44] of 847 patients operated on for Graves' disease, 25 (3·0 per cent) were shown to

Table 3 Frequency of multifocal disease in autopsy studies

Country	Multifocal disease (%)	Tumour size (cm)
Argentina[19]	27·3	1·0
Chile[17]	30·4	1·0
Finland[15]	27·8	1·5
Germany[18]	47·1	1·0
Tokushima, Japan[21]	30·4	1·0
Minsk, Belarus[23]	31·6	1·0
Spain[22]	27·3	1·5
Sweden[13]	20·0	1·0
Minnesota, USA[10]	32·4	1·5

Table 4 Rate of small papillary thyroid carcinoma in thyroidectomy specimens in different countries

Reference	Country	Presence of tumour in thyroidectomy specimens (%)	Tumour size (cm)
Delides *et al.*[24]	Greece	1·8	1·0
Park *et al.*[40]	Korea	5·1	1·0
Pelizzo *et al.*[41]	Italy	10·5	1·0
Ahuja and Ernst[42]	Germany	2·4	1·5
Terzioglu *et al*[43]	Turkey	2·2	1·0
Yeo *et al.*[39]	Singapore	0·8	1·5
Olen and Klinck[38]	Washington, USA	1·3	1·0

Table 5 Relationship of thyrotoxicosis and small papillary thyroid carcinoma in thyroidectomy specimens from different countries

Country	Graves' disease (%)	Toxic multinodular goitre (%)	Toxic adenoma (%)	Tumour size (cm)
Korea[40]	3·8	9·2	4·3	1·0
Italy[41]	5·7	0	2·5	1·0
Turkey[43]	0	2·2	0	1·0
Singapore[39]	0·6	0·3	0	1·5
Illinois, USA[45]	2·6	—	—	1·5
Japan[44]	3·0	—	—	1·5

have SPTC. There were no recurrences or deaths from thyroid cancer observed in this group, and the authors concluded that there was no relationship between increased growth of tumour and thyrotoxicosis[44]. The relationship between thyroid cancer and thyrotoxicosis is of particular interest because thyroid stimulating hormone (TSH) is thought to be an important factor in promoting growth and possibly genesis of thyroid carcinoma[43]. In rodents, TSH stimulation of the thyroid gland by goitrogenic diets leads to glandular hyperplasia and later neoplasia[46]. Because serum TSH levels are low or suppressed in Graves' disease and thyroid-stimulating antibodies are present, one possibility is that these antibodies play a role in stimulating thyroid cancer growth and invasiveness[47].

Papillary microcarcinoma and irradiation of the thyroid gland

The initial recognition that irradiation of the head and neck predisposes to the subsequent development of carcinoma of the thyroid gland was first made by Duffy and Fitzgerald[48]. Following the dropping of atomic bombs on Hiroshima and Nagasaki, Sampson and colleagues had a unique opportunity to examine the thyroid glands at autopsy of large numbers of people who had lived in and around these cities. They found 536 carcinomas of the thyroid at 3067 autopsies (17·5 per cent) and 97 per cent of these were SPTC; the increased prevalence of SPTC was seen in persons exposed to 50 cGy or more[7]. Wagner *et al.*[49] examined 150 patients who had received head and neck irradiation in early life to the thymus, tonsils or adenoids, or for acne. Almost two-thirds had been irradiated between the ages of 2 and 6 years, with a latent period between irradiation and thyroid surgery of 20–30 years. The total number of thyroid cancers was 48 (32 per cent), of which 13 (27·1 per cent) were PMCs[49].

Following another disaster, the reactor accident at Chernobyl in April 1986, autopsies have been performed on the permanent residents of the region of Minsk who died in 1990 and 1991. The incidence of PMC in the age group 19–88 years was 8·8 per cent[23], a rate similar to the 9·1 per cent of SPTC found by Fukunaga and Yatani[11] in 1975 in nearby Polish residents; both studies used 2–3-mm sectioning of macroscopically abnormal areas of the thyroid gland. This indicated that there was no significant increase in the frequency of PMC in adults in the region of Minsk compared with other nearby countries. This finding is in sharp contrast to the 86 thyroid carcinomas presenting in children living in the Republic of Belarus after the Chernobyl disaster[21]. There was a mean interval of 4·4 years between the accident and the detection of these tumours; only ten (12 per cent) had a diameter of less than 1·0 cm. The conclusion from the more recent studies is that, although exposure to radiation almost certainly increases the likelihood of developing papillary thyroid cancer, the tumours will usually be larger than 1·0 cm and thus, by definition, not PMC.

Natural history of papillary microcarcinoma of the thyroid

The supposition that, with time, PMC will inevitably increase in size to become a clinically significant thyroid carcinoma is refuted by autopsy studies that show no increase in the prevalence of PMC with increasing age[7–24]. Furthermore, if the progression scenarios were true, one would expect high rates of papillary thyroid carcinoma in countries with high rates of PMC, but this is not the case. In Japan, a country with a high incidence of PMC, the rate of thyroid cancer is equivalent to that in the USA[10].

A second supposition, that PMC has a different biological behaviour to other forms of papillary thyroid cancer, is suggested by differences in prevalence between the sexes. PMC is present equally in both sexes but clinically apparent papillary thyroid malignancy is more common in women[2].

Long-term results of treatment of patients with papillary microcarcinoma

The results for this selected group of patients are shown no better than in the prolonged follow-up studies from the Mayo Clinic[6,32,50]. Woolner *et al.*[6] collected data on 140 patients (94 females and 36 males) treated at the clinic between 1926 and 1955. The mean age in the entire series was 40·5 (range 6–72) years. The most common clinical presentation was a mass in the lateral neck that had been present for between 2 weeks and 11 years (mean 2 years 9 months). However, in 82 cases (59 per cent) the diagnosis of SPTC was incidental, the thyroid gland being removed for other pathology. Cervical lymph node metastases were found at presentation clinically in 58 patients (41 per cent). There were no distant metastases. The smallest tumour focus to metastasize to lymph nodes was 3 mm. The jugular chain was the commonest group of nodes involved, followed by the tracheo-oesophageal group and nodes within the vicinity of the thyroid capsule. Multiple nodes were involved in the majority (90 per cent) of node-positive patients.

The node-positive and node-negative groups of patients were compared; there was no difference in the size of the tumour focus between metastatic and non-metastatic disease. There were no differences in the invasiveness of the primaries in the two groups, although psammoma bodies were seen in two-thirds of the node-positive group and in only one-third of the node-negative group[6]. Prolonged follow-up of the 140 patients for up to 30 (minimum 4) years revealed no known recurrences, irrespective of presentation, and no deaths from thyroid disease, with only one patient being lost to follow-up[6]. However, Hubert *et al.*[50] in 1980 reported on the same group of patients, commenting that 10 per cent had required further surgery. Some 18 per cent of node-positive patients had required further surgery, compared with only 5 per cent of node-negative patients.

The relatively 'benign' behaviour of PMC was disputed by Ardito *et al.*[51] in 1982. In a retrospective analysis of the results from 1117 thyroidectomy specimens, ten cases of SPTC were identified. Eight patients presented with neck nodal metastases, one with bone metastases, and one with bone and pulmonary metastases. The mean age of the patients was 30 (range 14–68) years. There were six females and four males. After operation two further patients developed distant metastases. The authors' conclusion was that the biological behaviour of SPTC was no different to that of clinically apparent papillary thyroid cancer, but throughout the paper the exact size of each tumour was not stated[51].

The most recent report from the Mayo Clinic[32] on the follow-up of 535 patients with PMC was reported in 1992. The mean overall length of follow-up was 17·5 (range 0·1–48·3) years. There were 373 women and 162 men with a mean age of 45 (range 6–85) years at presentation. The median tumour size was 8 mm; 172 patients (32 per cent) presented with cervical lymph node metastasis and one had distant metastases. Some 99 per cent of the tumours were histological grade 1, 20 per cent were multifocal and 2 per cent showed evidence of extrathyroidal invasion at surgery[32]. There was a 6 per cent rate of recurrence (27 patients) at 20 years; only two of 27 had a recurrence beyond 25 years with the majority occurring within the first 10 years. The presence of metastases within the cervical lymph nodes at presentation was significant. The rate of recurrence in the node-negative group was 1 per cent, while that in the node-positive group was 18 per cent ($P < 0.0001$). Local (thyroid bed) recurrences were unusual but were found by 10, 20 and 30 years in 0·6, 2·0 and 3·6 per cent respectively. Only two deaths directly related to thyroid malignancy were observed in the group of 535 patients. In 92 of the PMCs flow cytometric DNA ploidy determination was performed. Sixty-nine (75 per cent) were DNA normal (diploid), 11 (12 per cent) were tetraploid and 12 (13 per cent) showed evidence of DNA aneuploidy. The tumours of the two patients who died were found to be DNA aneuploid. The conclusion from this prolonged follow-up was that the presence of regional cervical node metastasis does not affect overall survival, and that PMC is a slow-growing lesion which rarely spreads to distant sites and which carries an overall good prognosis[32].

The most recent retrospective data on a large group of patients with PMC come from Noguchi's thyroid clinic in Japan[52]. This group reported on 867 patients (764 women and 103 men) aged 11–83 (mean 43) years, with a mean follow-up of 12·8 years. Thirty patients had clinically palpable neck nodal metastases and 17 had microscopic metastases. Recurrence in thyroid remnants was seen in five patients, as was recurrence in cervical lymph nodes. Two patients died with recurrent thyroid cancer[52].

The presence of cervical node metastasis is a well recognized presentation of PMC. The tumour growth within lymph nodes can be rapid, outstretching the blood supply, leading to cystic necrosis and degeneration of the node[53,54]; indeed, many lateral neck node metastases have in the past been mistaken for branchial cyst remnants[55,56]. The slow-growing nature of papillary thyroid carcinoma is well demonstrated by a report of a lateral cervical cyst in a 37-year-old woman, which was present for 14 years before the correct diagnosis of nodal metastasis from a 1·2×0·6×0·5-mm SPTC was made[57]. On occasion, finding the thyroid primary responsible for cervical lymph node metastasis is difficult, requiring meticulous pathological sectioning. The smallest reported PMC presenting with a metastasis in a scalene lymph node[58] was 0·2×0·3×0·6 mm in size and required 1375 sections at intervals of 50 μm.

The first report in 1970 of a distant metastasis from PMC was of a solitary vertebral column lesion from a thyroid primary of 8·5-mm diameter[59]. Since then other distant metastases from PMC have been reported; these include other skeletal sites[60,61] and lungs[60,62]. Allo *et al.*[63] in 1988 presented seven case reports in which patients with impalpable tumours (maximum diameter 11 mm) had varying degrees of nodal metastasis at presentation associated with unencapsulated multifocal disease. This group concluded that PMC behaves like its palpable counterpart, having a high propensity to recurrence and exerting significant morbidity, if not mortality, in some cases. PMC with the worst prognosis is unencapsulated, multifocal, invasive and locally metastatic at presentation[63].

Preoperative diagnosis of papillary microcarcinoma of the thyroid

The diagnosis of PMC, like that of any malignancy, is based on clinical examination, laboratory investigations and specialized radiological techniques. With the advent of improved imaging techniques and FNAC, the diagnosis can now often be made before operation. It was recognition of this fact that led Salvadori *et al.*[64] to question the term 'occult'. They presented a series of 72 patients, 21 of whom presented with a palpable nodule in the thyroid. In 35 patients the thyroid primary was impalpable and, therefore, clinically occult. Of these, malignancy had been suspected because of palpable, suspicious regional nodes, and detected at radioiodine scintigraphy and/or ultrasonography (except in three patients). Regional enlarged lymph nodes were evident at clinical examination in 49 patients (68 per cent); in 35 of these, enlarged cervical nodes were the first and only sign of disease. Metastatic involvement was demonstrated by FNAC in 31 cases and confirmed by frozen section in 14. This study[64] demonstrates all the methods available to assist in the diagnosis of PMC and highlights the significant contribution made by the development of fine-needle cytological techniques.

The usefulness of such techniques was also demonstrated by the Mayo Clinic follow-up study between 1940 and 1989[32], in which FNAC was introduced in 1980. In the period between 1940 and 1979, the diagnosis of PMC was made at thyroid operation in 70 per cent of cases, by open lymph node biopsy in 19 per cent and was an incidental finding in 11 per cent. In the period from 1980 to 1989, FNAC was responsible for the diagnosis in 40 per cent of cases The diagnosis at thyroid operation fell to 20 per cent, the open lymph node biopsy rate was 22 per cent and the incidental finding rate was 18 per cent[32]. The discovery of nodules within the thyroid gland by palpation is dependent on patient characteristics and the experience of the examiner. Thyroid masses with a diameter of 0·5 cm may be palpated in a patient with a long thin neck, whereas nodules greater than 2·0 cm may be missed in a short fat neck. Witterick *et al.*[65] showed that, even in experienced hands, 160 (76 per cent) of nodules detected by pathological examination were missed by palpation. Twenty-four of these impalpable tumours were PMC of median diameter 0·3 cm. Ultrasonography failed to detect 120 nodules (57 per cent) in 50 patients. Twenty-two (18 per cent) of the missed nodules were PMC of median diameter 0·25 cm.

The advent of FNAC has greatly increased the frequency of preoperative diagnosis of PMC in two clinical settings. First, in patients who present with enlarged cervical lymph nodes, a preoperative cytological diagnosis can be obtained and the presence of metastatic thyroid cells within these nodes can prompt surgical excision of the involved thyroid gland. Second, if a PMC within the thyroid gland is close to the capsule, it may be palpated clinically and subjected to aspiration cytology. Recently, ultrasonographically guided FNAC has been used for impalpable lesions that are nevertheless thought suspicious on insonation. Rosen *et al.*[66] examined 59 patients referred for ultrasonographically guided fine-needle aspiration biopsy of the thyroid. About 70 per cent of the group (41 patients) were referred for surgery, which revealed cancer in 15 (four tumours smaller than 1·0 cm). Ultrasonographically guided FNAC yielded false-positive reports in no patients, false-negative reports in 12 per cent and inadequate aspirates in 32 per cent. The ultrasonographically guided technique had a relative sensitivity of 60–90 per cent, a specificity of 100 per cent, a positive predictive value of 100 per cent, a negative predictive value of 80 per cent and an accuracy of 85 per cent. It provided cytological information in 60 per cent of patients in whom a diagnosis could not have been made by orthodox means[66].

A diagnosis of thyroid malignancy may be difficult using haematoxylin and eosin staining of the few cells obtained from FNAC. A more definitive diagnosis can be made by means of immunohistochemical staining with antithyroglobulin antibodies, as thyroglobulin is specifically present in the follicular cells of the thyroid gland[67]. This method has proved clinically impractical because it is a time-consuming and complex laboratory procedure. However, a rapid immunoperoxidase method has been described which requires only a 5-min staining time[67]. This faster method has proved useful in preoperative and perioperative settings in the diagnosis of PMC. There are no special differences between PMC and clinically manifested papillary cancer in the location of cytoskeletal proteins and thyroglobulin[68], but immunoreactivity for epithelial membrane antigen may prove useful in the recognition of metastatic thyroid cancer at initial diagnosis[69].

Surgical treatment of papillary carcinoma of the thyroid

The treatment of differentiated papillary thyroid cancer has been hotly debated down the years by protagonists for a conservative surgical approach (lobectomy)[64,70–73] and those for an aggressive surgical approach (total thyroidectomy)[4,5,74–76], with many others adopting intermediate positions[2,32,52,77–79]. The low mortality rates associated with papillary carcinoma make assessment of therapeutic efficacy difficult and so recurrence rates are employed. Although many series[4–6] have shown that the presence of cervical node metastases at presentation increases the risk of further nodal recurrence, it does not increase mortality; this has been refuted in one retrospective study of age- and sex-matched groups[80]. Prognostically important areas of recurrence are invasion of adjacent structures in the neck (extrathyroidal spread), recurrence in the thyroid bed or remnant, and distant metastases[2]. Noguchi *et al.*[52] showed that extrathyroidal extension of the primary tumour was associated with a significantly higher recurrence rate. The low morbidity and long survival with this tumour mean that collection of randomized prospective data has never been performed and hence the comparisons of therapies are based on retrospective studies[2,4,32,52,64,70–82].

The surgical approaches to the treatment of papillary thyroid carcinoma are varied, but the main choices are between lobectomy and near-total or total thyroidectomy. The main argument against total thyroidectomy is the increased rate of complications with which this operation is associated. While the incidence of permanent recurrent laryngeal nerve injury of 0–7·9 per cent[2,75,76,81,83–85] is similar for both procedures, that of permanent hypocalcaemia, because of damage to the parathyroid glands, varies substantially. The incidence after subtotal surgery is 0–0·3 per cent[2,81], compared with 2–32 per cent[2,74,75,82,83,85] following total thyroidectomy. In skilled hands total thyroidectomy can be performed with acceptable complication rates with postoperative radioiodine scans indicating thorough surgical ablation in the majority[85]. The proponents of total thyroidectomy recommend its use in papillary thyroid cancer because it eliminates multifocal disease, the possibility of transformation of a remnant recurrence from well differentiated to undifferentiated, decreases the overall recurrence rate and allows metastases to take up radioiodine (^{131}I)[76]. They add that reoperation on the neck for recurrence can be difficult and that the complication rate may double[86].

Multifocality is well recognized in papillary thyroid cancer, but the numbers of remnant recurrences observed in conservatively treated groups have not matched the number predicted if all the microscopic foci of papillary cancer in the untreated lobes were to have grown[72,81].

Prognostic scoring systems for papillary thyroid cancer

To guide surgical therapy for papillary thyroid carcinoma a number of prognostic scoring systems[87–90] have been developed for perioperative use. These are based on multifactorial analysis of retrospective data from all papillary thyroid cancers. The first prognostic scoring system for papillary thyroid cancer from the Mayo Clinic was the AGES score[87]. This was based on the Age of the patient at presentation, Grade of the tumour, Extent of the tumour at surgery and Size of the primary. Patients were grouped into minimal risk (AGES score less than 4) and high risk (AGES score 4 or more)[87]. Using this system it was shown that lobectomy and isthmectomy was appropriate for groups at minimal risk, but ipsilateral lobectomy plus contralateral subtotal lobectomy was superior for high-risk groups. In neither the minimal nor the higher risk group was survival improved by the performance of total thyroidectomy[87]. However, in a follow-up study based on this scoring system, local recurrence was shown to be significantly higher in the lobectomy group and revised recommendations were for some form of bilateral thyroid surgery in both groups[79]. The AGES system was then simplified by the Lahey Clinic group to the AMES system[88]: Age, Metastases to distant sites other than lymph nodes, Extent of the primary tumour and Size. The features that placed patients in the high-risk groups were age over 40 years in men and over 50 years in women, distant metastasis and size greater than 5 cm.

Patients in the low-risk group made up 90 per cent of cases and again the recommendation was for bilateral thyroid surgery but not total thyroidectomy[88]. The next modification to scoring was the addition of DNA ploidy (DAMES)[89], as this had been shown to be a powerful prognostic factor, with aneuploidy conferring increased risk of distant metastases and death. The proponents of DAMES could obtain accurate DNA analysis on FNAC and intended that the scoring system be used during operation[89].

The AGES score was not used widely because of differences in pathological grading between pathologists, and the Mayo Clinic group considered that DNA ploidy estimations, although undoubtedly useful, were time consuming and expensive[90]. This led to the development of the latest prognostic scoring system, MACIS[90], which uses five variables: Metastasis, Age, Completeness of resection, Invasion and Size. Unfortunately this score can be used only after the primary operation.

Treatment of involved cervical lymph nodes in papillary thyroid carcinoma

The incidence of cervical lymph node metastasis at presentation of PMC is considerable (32 per cent)[12]. There is evidence that simple 'node picking'[5,32,52] of grossly affected nodes at operation is as effective as radical[70] or modified radical[80] neck dissection in the control of recurrent disease. The morbidity and poor cosmesis following radical neck dissection is too great to recommend its routine use and there is a significant increase in the rate of postoperative permanent hypocalcaemia, from 3 to 15 per cent, if neck dissection is added to total thyroidectomy[91]. While micrometastases in cervical lymph nodes can certainly be demonstrated[92] in papillary thyroid cancer, their presence is not biologically significant and prophylactic neck dissection cannot be recommended as some have suggested[70].

Adjuvant treatment for papillary thyroid carcinoma

The two main adjuvant therapies are the postoperative administration of radioiodine (^{131}I) and the lifelong administration of thyroxine to suppress TSH. The use of postoperative external-beam radiotherapy, once popular[80], has no place in the treatment of well differentiated thyroid cancer and may even be deleterious[5]. It has been recommended that the treatment of well differentiated papillary thyroid cancer should not be conservative and that postoperative ^{131}I and suppressive doses of thyroxine should be routine[74]. While some advocate the routine use of ^{131}I and thyroxine[4,5,93] because it reduces the rate of recurrence[5], others use thyroxine alone, preferring ^{131}I only when metastatic disease becomes apparent[2,32,52,78,82].

Treatment of papillary microcarcinoma of the thyroid

Most of the retrospective reports discussed so far relate to all papillary thyroid cancers. From some of these studies information specific to PMC can be extracted[4,5,73]. This will now be discussed together with the few papers dedicated to the treatment of PMC alone[32,49,52,64,93]. The recommendations for treatment of this tumour subgroup vary widely. Ito *et al.*[72] concluded that no specific treatment was necessary for this type of tumour except its simple excision. They added that 'microcancer has few clinical characteristics of carcinoma with regard to preoperative diagnosis, treatment and prognosis'. On the other hand, Salvadori *et al.*[64] recommended total thyroidectomy, radioiodine and suppressive doses of thyroxine, concluding that 'occult papillary cancer does not differ from other papillary cancers with respect to morphological, clinical and prognostic factors – it differs only in size'. The most recent data from the Mayo Clinic[32] suggest that ipsilateral lobectomy and contralateral subtotal lobectomy, leaving a 1–2-g remnant, combined with simple excision of involved nodes, is the approach of choice, with no benefit being gained from total thyroidectomy. While some agree with this[5,52], others have shown that radical surgery does not influence recurrence and recommend lobectomy and isthmectomy[4,73]. With respect to adjuvant therapy the consensus appears to be the routine use of thryoxine to suppress TSH, but not the use of radioiodine[5,32,52,73] as there is no difference in the recurrence rate.

The most recent data from the Lahey Clinic[93], based on the AMES prognostic scoring system, split patients with PMC into two groups: women aged 50 years or younger and men of 40 years or less (low risk), and the older age groups (high risk). The recommendations for the low-risk group are conservative thyroid surgery, modified or limited node dissection and thyroid suppression. The recommendations for the high-risk group are bilateral thyroid surgery, modified or limited node dissection, thyroid suppression and radioactive iodine[93]. This is in contrast to the Noguchi thyroid clinic, which recommends conservative bilateral surgery, 'node picking', thyroid suppression and long-term follow-up only[52].

Therapeutic recommendations

It is difficult to group all PMCs together and recommend one approach based solely on size as there are many varied presentations of this disease. It is, however, an absolute requirement that the treatment of PMC should not cause more morbidity than the disease process itself. To this end, it is the authors' belief that the care of patients with thyroid cancer, if total thyroidectomy is to be achieved with an acceptable level of morbidity, should not be undertaken by the occasional thyroid surgeon. Taking into account all opinions expressed in the published literature, the following therapeutic recommendations are offered.

1. *Neck nodal metastases (papillary thyroid cancer confirmed by FNAC or biopsy) and no primary lesion identified.* Total or near-total thyroidectomy, 'node picking' and TSH suppression, await pathology findings. If PMC excised completely, regular follow-up only.
2. *Neck nodal metastases and site of PMC known before operation.* Ipsilateral lobectomy and contralateral subtotal (or total) lobectomy, 'node picking' and TSH suppression. If the paratracheal nodes are involved they should be excised. If PMC excised completely, regular follow-up only.
3. *PMC known before operation and no nodes in a patient aged 39 years or less.* Ipsilateral lobectomy and isthmectomy, with intraoperative palpation of the

opposite lobe and subtotal excision if abnormal, and TSH suppression. If PMC excised completely, regular follow-up only.

4 *PMC known before operation and no nodes in a patient aged 40 years or more.* Ipsilateral lobectomy and contralateral subtotal lobectomy, and TSH suppression. If PMC excised completely, regular follow-up only.

5 *Incidentally discovered PMC in thyroid excised for other pathology.* If the patient is low risk for age and the tumour is excised completely with no nodes, regular follow-up is advised, although this is of questionable value. If high-risk age group, incomplete incision, nodal metastasis in retrospect or DNA aneuploid tumour (if available), give TSH suppression. Offer further treatment, re-exploration or radioiodine after discussing prognosis with patient.

6 Occasionally multifocal PMC will be identified either as a dominant lesion with other foci or multiple foci. The biological significance of multifocal lesions is unclear and there is no clear recommendation for treatment. The approach to such patients is likely to reflect the treatment philosophy of the individual surgeon.

7 A further issue is what to tell the patient with an incidentally discovered PMC. Only Frauenhoffer *et al.*[71] have commented on this, suggesting that carcinoma should not be mentioned in younger patients who have a completely excised PMC. They added that the 'benign' behaviour of these tumours may not warrant the potential social and economic complications of a 'cancer' diagnosis. This approach may be unacceptable to some practitioners; it is an issue for the individual surgeon to decide on.

In summary, PMC of the thyroid is not uncommon and is associated with a good or excellent prognosis. The nature of surgical therapy should depend on the clinical presentation, and must be achieved with minimal morbidity to the laryngeal nerves and parathyroid glands.

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British Journal of Surgery 1996, 83, 1684–1688

Review

Oesophageal function testing and antireflux surgery

G. McLAUCHLAN

Department of Surgery, West Coast General Hospital, 3841 Eighth Avenue, Port Alberni, British Columbia, Canada V9Y 4S1
Correspondence to: Dr G McLauchlan

Despite the increasing emphasis that is placed on both pH measurement and oesophageal manometry, there is little consensus about their usefulness in the clinical setting. These tests are far from infallible and it is difficult to support their universal application in patients with gastro-oesophageal reflux disease. Nevertheless, these imperfect tests are useful in certain situations and clinicians must strive to use them intelligently for those most likely to benefit.

Since the introduction of laparoscopic antireflux surgery with its associated reduced hospital stay and early return to full activities, a wave of enthusiasm for this procedure has swelled to the point where it is being proposed as a reasonable alternative to long-term medical therapy. To defend this position adequately, the surgeon will have to detail the indications and outcomes carefully. Indeed, this demand for perioperative documentation for operations both new and old may well be one of the major spin-offs of the widespread adoption of laparoscopic techniques into general surgery.

In the case of gastro-oesophageal reflux disease (GORD), this reopens the debate on appropriate preoperative and postoperative assessment. It is becoming an accepted belief that, to minimize the risk of a poor outcome, a full physiological assessment of oesophageal function is mandatory in every case. But how much is enough?

Oesophageal function testing and antireflux surgery

Many investigations can be used to supplement clinical evaluation in the patient with suspected GORD: endoscopy, barium studies, manometry, 24-h pH monitoring and scintigraphy. The first two are readily available and commonly used. The last is neither. Regarding the relevance of manometry and pH monitoring in the perioperative setting, two respected groups have summarized their positions as follows. Mughal *et al.*[1] have written: 'We therefore offer the reassurance that Nissen fundoplication may be safely performed in those patients who are genuinely refractory to vigorous medical treatment regardless of the subtleties of preoperative manometry or pH recording'. But according to Mattox and co-workers[2]: 'Proper preoperative evaluation of patients being considered for antireflux surgery should include esophageal manometry and 24-hr esophageal pH studies. Failure to do so may result in a poor clinical outcome'.

Obviously both cannot be right. It is important for the surgeon to understand exactly what information these tests provide (*Fig. 1*).

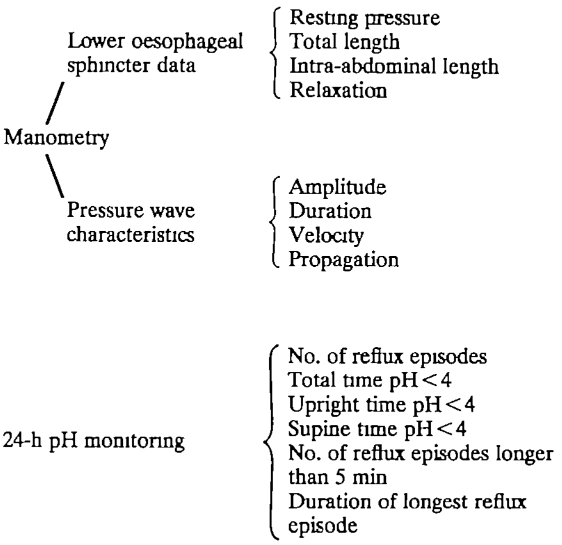

Fig. 1 Information provided by tests of oesophageal function

Aim

This review focuses on manometry and 24-h pH monitoring and questions objectively their importance to the surgeon. In deciding on the usefulness of a test, the criteria will be: (1) Does it give us a diagnosis? and (2) Does it influence our decision to operate or help to determine which operation?

Upper oesophageal sphincter pressure is not discussed in this review. For many reasons it is impossible to define a meaningful 'normal' range[3] and this measurement is seldom used in decision-making for antireflux surgery.

Manometry

Lower oesophageal sphincter

Resting pressure. Resting pressure is not easy to measure[4] and different methods are used[3,5–7], resulting in a considerable variation in 'normal' values[3]. Even using a single technique, there is widespread variation in the same individual on the basis of radial asymmetry[8,9], emotion[10] or conditioning[8]. In GORD it has been variously described as being lower than normal[11], no different from normal[8,9,12], not necessarily low[13,14], no different from normal unless severe oesophagitis is present[15] and

Paper accepted 19 July 1996

dependent on the severity of the reflux[8]. A widespread view is that mean lower oesophageal sphincter pressure (LOSP) is low in patients with GORD but that there is substantial overlap with normal values[4,5,9,15–21]. Pope *et al.*[9] have stated that LOSP provides information on the potential for reflux but gives no information about the actual presence of reflux or its complications. This is further complicated by the realization that resting tone does not necessarily reflect tone during reflux, which is believed to be due to phasic relaxation of the sphincter[4,6,13,22–24]. There is, therefore, no agreement about the importance of resting LOSP[8].

What is the value of preoperative LOSP measurement? It has been stated that, in a patient with GORD, surgery should not be done if preoperative LOSP is normal[25] or high[26]. Other reasons for reflux should be sought, for example poor oesophageal motor function or delayed gastric emptying in the presence of which 'fundoplication is strictly contraindicated'[27]. If these claims are true, the authors fail to provide examples to support them. Mughal *et al.*[1] found a low LOSP to be of poor predictive value and 90 per cent of their patients had surgery despite a 'competent' LOS.

There is no exact correlation between LOSP after operation and symptoms[13,28]. In a study comparing Nissen with Toupet fundoplication there was no difference in clinical outcome, despite the postoperative LOSP being significantly lower with the Toupet than with the Nissen wrap[29]. Postoperative LOSP has been found to increase[30], possibly due to artefact[5], to remain unaltered[31], or even to decrease[32] in a substantial proportion of patients who still have a good symptomatic result. It would appear that an operation cannot be described as 'good' on the basis of postoperative resting LOSP.

Other characteristics of the lower oesophageal sphincter. The remaining LOS measurements generally receive less attention than resting LOSP. Postoperative measurements of total sphincter length have been reported as identical to[30] and significantly greater than[33] preoperative values. As expected, intra-abdominal sphincter length is diminished before operation and restored to normal values after operation[30,33]. Sphincter relaxation must be complete before operation to exclude achalasia, and after operation may still be complete[31] but not necessarily in all patients[30].

Pressure wave characteristics

Amplitude. In patients with GORD the amplitude has been variously reported as normal[34], low[4,11,35], and low but with a large overlap with normal[15]. It has been hypothesized that reflux may reduce the amplitude[36,37] especially if oesophagitis is present[15], although the role of oesophagitis is unclear[35]. Postoperative improvement[21,38] and even complete return to normal[5] have been recorded. The chances of recording an increase in amplitude after operation may be greater if the preoperative value has not dropped below a critical level[38].

Duration. This has been described as normal[34,35], diminished in a direct correlation with peristaltic amplitude[15] and diminished before surgery with a return to normal after surgery[5].

Velocity. This has been said to be normal[34], slow with or without oesophagitis[15,35], and slow before operation, improving but still low afterwards[5].

Propagation. Failed propagation is not uncommon in normal individuals[3]. More severe abnormalities in patients with GORD are common[15], especially with oesophagitis, but this is neither necessary nor sufficient to establish the diagnosis[5]. Abnormalities in propagation have been advanced as being a contraindication to surgery[27]. It has also been stated, albeit with no supporting evidence, that good preoperative peristaltic activity leads to less dysphagia after operation[4,13,16,39], but this is not universally accepted[1,21,35,40]. Postoperative improvement has been documented[33,41] and, in one study, even when there was a postoperative increase in aperistaltic contractions from 34 to 53 per cent, the clinical outcome was not affected[5].

Summary of usefulness of manometry

Manometry can support but not make a diagnosis of GORD. If manometric findings are abnormal in an asymptomatic subject, will he or she eventually develop reflux? If findings are normal in the presence of reflux symptoms, will they become abnormal? The answers are 'no' and manometry is not, therefore, predictive[19].

Would the universal use of manometry prevent surgery on patients with other problems? Some authors believe that it would[26], but many others disagree. It is impossible to over-emphasize the importance of taking a detailed history[13,42], which should alert the clinician to the possibilities of achalasia, scleroderma and 'end-stage' reflux[36].

Reports of disasters following fundoplication in patients with achalasia[2,43] are often cited as justification for routine preoperative manometry, but a closer look at such examples shows elements in the history, for example dysphagia, that were obvious contraindications to surgery without further investigation. Far from supporting universal manometry, these reports in fact do nothing to dissuade one from the alternative approach of selective manometry based on a careful history.

Does manometry affect surgical decision-making? Many centres modify surgery on the basis of preoperative manometry. The pressure wave characteristics are considered to be particularly relevant and the manometry is performed 'primarily to assess the functional motor capacity of the body of the oesophagus; measuring the LOSP is of secondary importance'[44]. If oesophageal 'function' is poor, and because peristaltic dysfunction may lead to impaired clearance[45], no wrap[46], an incomplete wrap[47,48] or a Belsey-type procedure[49] have their advocates. Waring *et al.*[47] admit that there are no data to support these approaches, simply a (very reasonable) desire on the part of the surgeon to minimize the likelihood of postoperative problems. However, Bancewicz and colleagues[36] did not find manometry useful for diagnosis or preoperative assessment, and in their study there was no relationship between preoperative motility disorders and postoperative dysphagia. At the root of these disparities lies the unanswered question as to whether motility disturbances are secondary to reflux, and, therefore, potentially reversible[5,21,33,50–54] or primary, i.e. causative[11,55–57].

Finally, it should be appreciated that manometry is not easy to carry out. Its performance may be regarded as an art rather than a science[17]. The currently available computerized systems, although elegant, do not dispense with the need for painstaking attention to detail and, even then, interpretation can be difficult, requiring a great deal of operator experience. It is still important to heed the advice of Pope[17], corroborated by others[18,42]: 'The physician who is in charge of a clinical motility laboratory, must be familiar with the physical and performance characteristics of the apparatus being used and must be able to recognize the many artifacts and normal variants of patterns that exist'.

In summary, it appears that we are still some way from a full understanding of the pathophysiology of GORD[5,11,20,56], and this should be recognized. A recent review from the American Gastroenterological Association[3] concluded that 'insufficient data presently exist to evaluate the benefit of the preoperative assessment of peristaltic function'. The idea of performing a test that is expensive[18,42], time consuming[18] and not cost effective[18,36] in every patient with suspected GORD does not seem reasonable.

Twenty-four-hour pH monitoring

Little has been published on the individual components of the 24-h pH monitoring system but, in summary, these can be divided into two broad categories: acid reflux measurement and oesophageal acid clearance measurement.

Acid reflux measurement

These measurements comprise the number of reflux episodes, and the total, upright and supine times of pH less than 4. In general terms these values are increased in patients with GORD but there is a significant overlap with normal values, even in the presence of oesophagitis[58]. It is not clear whether upright reflux is less important than[59] or equally important as[60] supine reflux.

Oesophageal acid clearance measurement

These measurements comprise the number of reflux episodes lasting longer than 5 min and the duration of the longest reflux episode. Both are increased in patients with reflux disease but, again, there is an overlap with normal[58].

Most of the published studies on pH monitoring use a scoring system that involves weighted considerations of the above components to provide clearer separation of normal from abnormal. The system of DeMeester *et al.*[59] is commonly used.

Sensitivity and specificity

The specificity of pH monitoring methods is high (from 90 per cent[59] to 96 per cent[39]): if the test is abnormal, reflux is usually present. However, this does not prove that reflux is causing the patient's symptoms and, for this reason, the concept of a symptom index has been devised[61] to provide a higher correlation between symptoms and reflux episodes. New and improved variations on this theme are the symptom sensitivity index[62] and the symptom association probability[63]. Another major problem lies with the sensitivity. According to some authors this is high (between 90 per cent[59] and 96 per cent[39]). Others disagree; the score has been found to be abnormal in only 41 per cent[58] or 37 per cent[64] of patients with classical reflux. In patients with symptoms suggesting reflux, the following has been found: a positive test in 88 per cent with endoscopic oesophagitis, 84 per cent with histological oesophagitis, 90 per cent with symptoms and oesophagitis, and 55 per cent with symptoms and normal endoscopic findings[59]. There is disagreement about the significance of this last finding. DeMeester and co-workers[59] claim that the other 45 per cent are unlikely to have reflux, but this is disputed[58,64]. False-negative rates have been reported in the presence of oesophagitis[56,65], symptomatic reflux[66], radiological reflux[34] and Barrett's oesophagus[65]. False-negative rates of 29 per cent[58], 23 per cent[67] and 33 per cent[34] have been recorded, even in patients with erosive oesophagitis. The problem is that all methods currently used to quantify temporal relationships between symptoms and episodes of GORD, as assessed by 24-h pH monitoring, have major shortcomings[63] and have been roundly criticized[68].

Value of perioperative measurement

It has been claimed that 24-h pH monitoring can be used not only to detect reflux but also as a guide to treatment. Patients with upright reflux alone may not require surgery and should respond to medical therapy. A trial of medical therapy may be used for those with supine reflux but, if reflux occurs in both upright and supine positions, surgery should be offered regardless of the symptoms[59]. pH monitoring has been presented as 'mandatory'[27]. No evidence for such claims is provided. Routine 24-h pH monitoring has been found to be of marginal benefit, except for patients without oesophagitis or for those in whom the diagnosis was in doubt[47]. The authors of the latter study also point out the lengthy, cumbersome and uncomfortable nature of the test. It may be of value in cases of respiratory[69,70] or cervical[71] symptomatology secondary to GORD. Others have found pH monitoring of no value for predicting the outcome of medical therapy[72], for selecting candidates for surgery, for choosing the type of surgery or for predicting the results of surgery[1,73]. In one study a 93 per cent response rate to treatment was found despite the pH score being abnormal in only 41 per cent[58]; in another study four of six patients with severe reflux and positive endoscopic findings but a normal pH score were asymptomatic after operation[65]. It is often stated that 24-h pH monitoring is a good 'quantitative' test[61], but this is obviously incorrect. It is also flawed by an inability to detect bile or alkaline reflux[14].

After operation the test seems to have little value. Of ten patients who were symptomatic after surgery only three had a positive score[65]; six of 58 patients had a positive score after operation and yet remained asymptomatic[32].

Conclusions

Despite the increasing emphasis being placed on pH measurement and manometry[74], it is clear that there is no consensus regarding the usefulness of these two studies of oesophageal function. Many believe them to be of no value in a classical case of GORD[8,13,14,18,58,64]. While others may not go so far, all are aware of the fact that these tests are not infallible[4,13,20].

It has been suggested that indications for such investigations include: indefinite intermittent symptoms[13], atypical symptoms[13,59], dysphagia[13,17,18,59,61], chest pain[13,17,18,59,61], GORD not controlled by medical or surgical therapy[13], stricture[13], severe typical symptoms associated with normal endoscopic findings[14,59], pulmonary symptoms[4,58,59,61,69], paediatric patients[59] and previous surgery with recurrent symptoms[59].

It has been stated[30] that 'the goal of surgical treatment for gastro-oesophageal reflux is the restoration of cardio-oesophageal competence'. This may be true, but current understanding of what constitutes cardio-oesophageal competence is incomplete. Furthermore, it is clear that the tools of manometry and 24-h pH monitoring, while undoubtedly useful in certain situations, are imperfect. To restrict surgery to patients with positive 24-h pH studies, low LOSP and good peristaltic activity[7,38,75] seems unduly harsh.

It is obviously desirable to use 24-h pH monitoring and oesophageal manometry in an intelligent fashion, and to target patients most likely to benefit from such techniques rather than adopt a 'blunderbuss' approach. The onus is on surgeons with access to oesophageal function testing who do large numbers of antireflux procedures to perform the necessary trials and replace conjecture with scientific data. As an example, the use of an incomplete wrap in the face of disordered motility may well be correct, but as yet this remains unproven. Until such studies are completed, the most important considerations are that symptom relief is obtained, the patient is satisfied and his or her quality of life improves[13,28,59,76,77].

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British Journal of Surgery 1996, 83, 1689–1690

SURGERY TODAY
The Japanese Journal of Surgery

Digest

Dr Keizo Sugimachi, Editor-in-Chief of *Surgery Today* (*The Japanese Journal of Surgery*), has selected from the April, May and June 1996 issues of his journal for this quarter's digest. A digest of *BJS* for the same period written by Mr Colin Johnson, European Editor, appears in the Japanese journal.

Infection

The time courses of serum complement levels and the severity of sepsis were compared in two groups of patients with sepsis, one in which the patients survived (surviving group) and one in which they did not (non-surviving group)[1]. The components of the complement system were measured at several time points after the diagnosis of sepsis had been established. A double-antibody radioimmunoassay was used to measure C3a, C4a and C5a; the latex agglutination test was used to measure C3 and C4; nephelometry was used to measure C5; and Meyer's 50 per cent haemolysis method was used to measure CH50. Following the diagnosis of sepsis, the levels of CH50, C3 and C4 were significantly lower in the non-surviving than in the surviving group, while the levels of C3a and C4a were significantly higher in the non-surviving group. C5a levels were significantly higher in the non-surviving than the surviving group, although no significant intergroup differences were subsequently noted. These results suggest that serum levels of C3a, C4a, C5a, CH50, C3 and C4 could serve as indices of the severity of sepsis. Thus, monitoring the complement system may be useful for predicting the outcome of patients with sepsis.

Interleukin-1 (IL-1), a cytokine released from macrophages by endotoxin stimulation, has been shown to upregulate the genetic expression of hepatocyte growth factor (HGF). A study[2] was conducted to determine whether plasma HGF is increased in patients with systemic inflammatory response syndrome (SIRS). The plasma levels of HGF, endotoxin and beta-glucan were measured in 41 surgical patients without hepatic disease, 18 of whom had been diagnosed with sepsis and 23 with non-septic SIRS. The plasma level of HGF was increased significantly in the 18 patients with sepsis and the 23 patients with non-septic SIRS, compared with values in 40 normal controls. No significant correlations were observed between the plasma levels of HGF and endotoxin or beta-glucan in any patient; however, plasma HGF was correlated significantly with the white blood cell count ($r = 0{\cdot}34$, $P < 0{\cdot}05$) and with total bilirubin ($r = 0{\cdot}45$, $P < 0{\cdot}01$). Plasma HGF was also strongly correlated with plasma alanine transaminase (ALT) level in eight patients with ALT levels higher than 50 units/l ($r = 0{\cdot}70$), but there was no such correlation in 33 patients with ALT levels of 50 units/l or less ($r = 0{\cdot}30$). Thus, although the clinicopathological significance of HGF is not well understood, the present findings indicate that plasma HGF increases in response to infection or inflammation.

Oncology

The role of insulin resistance in the tumour-induced decrease in tissue lipoprotein lipase (LPL) activity was studied *in vivo* and *in vitro* in methylcholanthrene-induced sarcoma-bearings rats[3]. Intraperitoneal injection of 2 units of regular insulin resulted in high-adipose LPL activity in control rats but had little effect on tumour-bearing rats. When adjusted for serum insulin concentration, adipose LPL activity remained significantly different between the tumour-bearing and control groups. Following *in vitro* incubation of adipose tissue fragments obtained from rats in both groups with either glucose 1·44 g/l or insulin 1×10^{-8} units, measurable LPL activity was maintained in the tissue from controls for 2 h but not in that from tumour-bearing rats. These results suggest that the decreased LPL activities seen in the tumour-bearing state may be mediated by insulin resistance.

Digestive surgery

To investigate further whether multiple genetic changes are involved in the development of colorectal cancer, Ieda *et al.*[4] performed an immunohistochemical analysis of *p53* and *ras* p21 protein expression in 139 specimens of colorectal adenoma with varying degrees of dysplasia, 57 specimens of early cancer with an adenomatous component, and 12 specimens of superficial early cancer with no adenomatous component. Positive *p53* staining was found in 15 per cent of the adenomas with moderate dysplasia and in 42 per cent of those with severe dysplasia or intramucosal carcinoma. Positive immunostaining of *p53* was observed to be significantly correlated with the degree of dysplasia and depth of invasion, as was the expression of *ras* p21. However, a closer correlation was observed with increasing size of the adenomas. Furthermore, *p53* staining was positive in five of the 12 superficial early cancer specimens, while *ras* staining was positive in only one. These results indicate that *p53* gene overexpression may play some biological role in both the adenoma-to-carcinoma sequence and in *de novo* cancer development, whereas *ras* p21 expression may not be as involved in *de novo* cancer development as in the malignant conversion of colorectal adenomas.

The results of treating 12 consecutive patients with irresectable colorectal hepatic metastases with a hepatic arterial infusion of high-dose Adriamycin (Kyowa Hakko Kogyo, Osaka, Japan) 100–120 mg/m^2 using hepatic venous isolation (HVI) and charcoal haemoperfusion (CHP) are reported[5]. Adriamycin was administered over 5–15 min under extracorporeal drug elimination by HVI–CHP. HVI was accomplished percutaneously by either the double-balloon technique using a Fogarty occlusion catheter (8/22 Fr) or a balloon-tipped catheter (16 Fr). During the infusion, isolated hepatic venous blood was filtered by CHP and pumped into the left axillary vein. There were no fatal complications, and good haemodynamic tolerance to HVI–CHP was confirmed. Tumour liquefaction, accompanied by a sharp decrease in serum carcinoembryonic antigen level by more than 50 per cent of pretreatment levels, was observed in six of the 12 patients 1 month after treatment. Apart from chemical hepatitis, which developed in 11 patients, Adriamycin toxicity was well controlled following the development of nausea and vomiting in two of 12 patients, leucopenia below 2000 per mm^3 in three and gastric ulcer in one. These results indicate that this method is a safe and useful procedure for otherwise hazardous high-dose intra-arterial chemotherapy in patients with irresectable hepatic tumours.

Thoracic surgery

The effect of the addition of albumin to crystalloid cardioplegic solutions was investigated in infants who underwent open heart surgery[6]. The patients were divided into four groups according to whether they received crystalloid cardioplegic solutions with or without albumin. Cardioplegic solution (Kurume solution: Kurume University, Japan) without albumin was administered to 12 patients (group 1); Kurume solution with 1 per cent albumin to ten patients (group 2); glucose insuline kalium (GIK) solution without albumin to ten patients (group 3); and GIK solution with 1 per cent albumin to 15 patients (group 4). All patients had a ventricular septal defect and underwent closure of the defect with Dacron (Meadox Medicals, Oakland, New Jersey, USA) double velours through either the tricuspid or pulmonary valve. The results showed that the percentage oxygen extraction in group 2 was significantly greater than that in group 1, while the value in group 4 was less than that in group 3, 5 min after reperfusion. No significant differences in muscle–brain creatine kinase were seen between groups 1 and 2, or between groups 3 and 4, for any measurement during reperfusion. However, significant differences in percentage lactate and malondialdehyde extraction values between the groups with and without albumin were noted 5 min after reperfusion. These results did not completely support the addition of albumin to crystalloid cardioplegic solutions to help preserve myocardial aerobic metabolism in infants; however, such an addition might contribute to the preservation of myocardial lactate utilization while also helping to inhibit lipoperoxide metabolism immediately after reperfusion.

Vascular surgery

In addition to the polytetrafluoroethylene (PTFE) vascular graft (G) with its conventionally smooth surface, a unique PTFE graft with a ridged outer wall (T) is now also currently available for clinical use[7]. Although an excellent antikinking property is provided by this unique outer structure, the possible influence of the structure on the formation of pseudointima has not yet been investigated in detail. Four kinds of T graft (3 mm inner diameter, 3 cm long) with various fibril lengths (FL; T-15, T-30, T-60, T-90) and a G graft with a 30-μm FL (G-30) were implanted into the inferior vena cava of rabbits. The patency of the grafts at 4 weeks was as follows: six of eight T-15, six of eight T-30, five of eight T-60, none of eight T-90 and four of six G-30. Pseudointimal hyperplasia of the T grafts advanced as the FL increased, judging by the thickness of the pseudointima, cellular density and maturity of fibroblasts. In addition, the maturity of endothelial-like cells on the luminal surface increased as the FL increased. The degree of pseudointimal hyperplasia in G-30 grafts was comparable to that of T-15 prostheses, although the maturity of the endothelial-like cells was similar to that of T-60 grafts. Microscopically, there was a microheterogeneity of cellular density in T grafts probably due to the uneven outer structure. In conclusion, not only FL but also the outer structure of PTFE may influence the formation of the pseudointima.

The effectiveness of monitoring somatosensory evoked potentials (SEPs) at operation to detect early brain damage remains controversial[8]. To assess the diagnostic accuracy of this modality, a study was conducted between 1991 and 1994, recording SEPs in 287 consecutive patients undergoing cardiac and aortic surgery using cardiopulmonary bypass with moderate hypothermia or deep hypothermic circulatory arrest. SEPs occurring within 50 ms latency in response to electrical stimulation of the median nerve were recorded over the contralateral postcentral cortex at 5-min intervals using a Neuropack-2 (Nihon Koden, Tokyo, Japan). Normal SEPs were recovered in 247 patients after operation; however, two of these patients had suffered a cerebral infarction and one a transient stroke at operation, demonstrating a false-negative incidence of 1·2 per cent. On the other hand, three different types of abnormal SEP were recorded after operation. Absence of P1 and N1, probably caused by a subcortical lesion, was observed in four patients; absence of P2 and N2, probably caused by a cortical lesion, was observed in eight patients; and a flat SEP, representing diffuse damage, was observed in two patients. Among these 14 patients with abnormal SEPs, seven showed no neurological disturbance at all, demonstrating a false-positive incidence of 50 per cent. Thus, Kawada *et al.* concluded that when normal SEPs are recovered during weaning from cardiopulmonary bypass, the incidence of brain damage could be predicted at below 5 per cent. Conversely, when abnormal SEPs are demonstrated, the incidence of brain dysfunction impeding a return to active life is estimated to be about 70 per cent.

K. Sugimachi

Editor-in-Chief
Surgery Today (The Japanese Journal of Surgery)
Department of Surgery II
Kyushu University
Fukuoka 812
Japan

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British Journal of Surgery 1996, 83, 1691–1693

Annales de Chirurgie

Digest

For this quarter's digest, Dr Denis Castaing, Editor of *Annales de Chirurgie*, chooses the best from issues three, four and five of 1996. A reciprocal digest written by our European Editor, Mr Colin Johnson, appears in the French journal.

General surgery

In general surgical practice, unexplained abdominopelvic pain is a real problem, because of the risk of recurrence or missing an important disease. Champault *et al.*[1] studied prospectively a series of 99 patients (67 women; mean age 25·5 years) admitted during 1991 and 1992 for acute abdominal pain in whom no aetiology was found. Follow-up was 100 per cent at 1 month, 98 per cent at 6 months, 95 per cent at 1 year and 84 per cent at 2 years. The patients were divided into three groups: 42 patients in group I underwent clinical, laboratory and radiological investigations only; 31 in group II underwent laparoscopy and the appendix, considered to be normal by the surgeon, was left in place; and 26 patients in group III underwent laparoscopic appendicectomy for an appendix apparently abnormal to the surgeon and later found to be normal by the pathologist. For 90 per cent of patients, the painful episode never returned. When the pain returned within 1 year, there was no difference in incidence between the three groups (11, 10 and 12 per cent). The reasons for the second admission were mostly genital or rare diseases (one patient with Crohn's disease at 3 months, one Spigelian hernia 1 year later). One patient in group I was operated on for acute appendicitis after 1 year. In those who had a laparoscopy (groups II and III), the incidence of persistent pain was identical whether the appendix was considered to be normal by the surgeon or found to be normal pathologically. The authors conclude that after admission for acute abdominal pain of unknown cause, the incidence of recurrence of pain is 10 per cent within 1 year; that it is possible to exclude (for 3 years) a serious abdominal or genital disease with investigations carried out during the patient's admission; that the risk of missing a true appendicitis is small (2 per cent) and has no prognostic significance; and that the finding of a normal appendix during laparoscopy should not inevitably lead to its removal. These conclusions suggest that 1-year follow-up is sufficient to assess the outcome of unexplained abdominal pain.

In a review of the recent literature, Stockle and Rivoire[2], from Lyon, try to define the place of surgical treatment (conservative surgery and radiotherapy) in the treatment of soft tissue sarcoma. The quality of surgical resection, defined by the resection margins, is the main risk factor for local recurrence. Combination with radiotherapy after inadequate surgery can improve local control, but cannot equal the results obtained after adequate surgery. Some limited tumours can be treated by surgical resection alone, but radiotherapy remains essential for more advanced tumours. Under these conditions, local recurrence rates after surgery alone, surgery and systematic radiotherapy and surgery with radiotherapy as required are 27, 28 and 30 per cent respectively. The development of local recurrence appears to affect the survival of patients with a tumour of good initial prognosis, particularly if it is an early recurrence. Serious postoperative morbidity is observed in 14 per cent of cases and is responsible for delayed complementary treatment and functional disorders. The use of muscle flaps to fill the surgical defects can reduce these complications. Evaluation of the functional results must be based on defined objective criteria.

Small bowel

François *et al.*[3], from Lyon, reported the morbidity of twisted loop ileostomy in a retrospective study of 83 procedures carried out in 79 consecutive patients between 1985 and 1994. There were 43 cases of ulcerative colitis, 13 of colon cancer, 12 of Crohn's disease, 12 of polyposis and three others. Before closure of the twisted loop ileostomy, three patients died from cancer progression and 13 (16 per cent) developed complications: seven cases of small bowel obstruction (8 per cent), four of high stoma output (5 per cent) and two of cholestasis. These complications required surgery in five cases. After stoma closure (performed in the 76 surviving patients), eight patients (11 per cent) developed complications, which required surgery in three: enteric fistula in four patients (5 per cent) requiring reoperation in two, occlusion in three, one occlusion (adhesiolysis) and wound suppuration in two. The authors conclude that this procedure adds a separate set of postoperative complications, which tend to be minor in nature without any permanent sequelae and which can be minimized by meticulous surgical technique.

Martel *et al.*[4] reported experience in the surgical management of radiation-injured small bowel. From 1978 to 1992, 55 patients (48 women) with a mean age of 62 (range 35–89) years underwent 70 operations for radiation injury of the small bowel. Primary pathology treated with radiotherapy included 40 gynaecological cancers (73 per cent), nine malignancies of the colon or rectum (16 per cent), four male genital cancers (7 per cent) and two carcinomas of the bladder (4 per cent). External radiation was performed alone in 47 patients (85 per cent) or associated with intracavitary radium or caesium (8–15 per cent). Mean radiation dose was 50 Gy for 35 patients and not specified but greater than 45 Gy for 20 patients. Fifteen patients had associated chemotherapy. The latent period between radiation injury and first symptoms was 39 months (range 1–16 years) and there were 72 months (range 3–26 years) between radiation and surgical treatment. There were 28 solitary lesions (mean length 148 cm) with five associated colic injuries, and 27 multiple lesions of the small bowel (mean length 187 cm) with 21 associated colic injuries. Twenty-one lesions of the abdominal wall and 13 lesions of the urinary tract were associated. Nineteen patients had preoperative total parenteral nutrition. Surgical treatment was performed for chronic obstruction in 46 patients, for fistulas in five or for an acute complication in four (three perforating peritonitis and one intestinal occlusion). Operations performed were 32 isolated small bowel resections, associated with bypass in two, 15 internal bypasses and six dissections of adhesions and/or stoma. There were two operative deaths (4 per cent). Complications occurred in 16 (29 per cent); there were three anastomotic fistulas. Functional results were good in 36 patients (24 resections and seven bypasses) and poor in two (one resection). Failure leading to a second operation occurred in 15 (five resections and six bypasses). The conclusions drawn from this important series are that preoperative nutritional assistance improves operative results and that intestinal resection is better than internal bypass whenever it can be performed without extreme risk or unacceptable sequelae.

Primary adenocarcinoma of the duodenum is a rare disease. Lachachi *et al.*[5] report three cases: two involving the duodenum and one the duodenojejunal junction. These tumours are characterized by polymorphic clinical signs, mostly non-specific pain or duodenal occlusion. Diagnosis is suspected by upper gastrointestinal endoscopy and barium swallow and confirmed by endoscopic biopsy. Whipple operation is the best curative procedure in the absence of local lymph node involvement. Cases of extensive invasion are managed by biliodigestive bypass. Prognosis is good, depending on histological differentiation and lymph node extension.

Colon and rectum

The complications of colostomy may constitute a handicap for patients: their prevalence, severity and methods of treatment remain poorly known. Andrivot *et al.*[6], from Brest, have analysed a series of 500 colostomized patients. Mean(s.d.) age was 66(14) years and mean(s.d.) follow-up of the study was 6(5) years. Colorectal cancers represented 65 per cent of the initial diseases. Sixty per cent of colostomies were terminal. They were performed for resection of the colon and/or rectum in 56 per cent of cases Thirty per cent of patients presented only one complication. Early complications, observed in 30 per cent of patients, were mostly benign and in the majority were local abscess and colon necrosis; 20 required emergency reoperation. Late complications, observed in 22 per cent of 391 patients with a follow-up of more than 1 year, were 30 incisional hernias, 28 prolapses, 24 distal stenoses and six others. These complications required another operation in one-third of cases. Complications of colostomy remain frequent (30 per cent) and the reoperation rate is between 13 (early) and 33 per cent (late complications). When reoperation is necessary, ideally it should be radical via a midline incision. The transposition technique gives better results than repositioning via a local approach. The therapeutic success rate of late reoperation is between 63 and 74 per cent.

In December 1994, the French Consensus Conference on the Treatment of Rectal Cancer stated that 'preoperative irradiation improves local control in patients with T_3 and T_4 resectable cancer and is recommended'. Recent data indicate that this approach not only reduces local recurrence but also increases overall survival. The therapeutic ratio of radiotherapy depends on the total dose delivered and technical local parameters. Inadequate radiotherapy techniques lead to increased toxicity and mask the potential benefits of the treatment. Levamisole and fluorouracil is a known adjuvant therapy. In a review on clinical oncology, Bosset *et al.*[7] extended the Consensus Conference recommendations to a combination of radiotherapy and chemotherapy (5-fluorouracil and levamisole) during the preoperative period to avoid the occurrence of metastasis. This is a logical association and a combined preoperative chemoradiotherapy trial is now under evaluation in a large European phase III trial (EORTC22921-FFCD9203).

Liver and biliary tract

A prospective and anonymous study[8] performed by the members of the Société Française de Chirurgie Endoscopique et Radiologie Opératoire, involving 150 French surgeons, aimed to evaluate the results of laparoscopic cholecystectomy in 1994. All 4624 patients who underwent cholecystectomy that was started laparoscopically were included (3310 women of mean(s.d.) age 42·5(19·8) years and 1314 men of mean(s.d.) age 56·3(16·1) years). There were 4261 laparoscopic operations (group I) and 320 conversions (group II). The conversion rate was 7·0 per cent. Intraoperative cholangiography was done in 74 per cent of patients in group I and 33 per cent of those in group II. Mean(s.d.) duration of the total procedure was 58·5(36·7) min. The morbidity rate was 5·0 per cent ($n = 230$): 4·8 per cent in group I ($n = 203$) and 8·4 per cent in group II ($n = 27$). Biliary complications occurred in 1·3 per cent of patients in group I, including 22 cystic duct fistulas and three bile duct injuries; the rate was 2·2 per cent in group II, including one biliary stenosis. The mortality rate was 0·2 per cent; there were four cases of peritonitis (one biliary), two of cardiac failure and one cerebrovascular accident. In two patients, the cause of death was not defined. It was concluded from these results that morbidity and mortality rates have not changed dramatically since the advent of the laparoscopic technique, whereas the frequency of common bile duct injuries has decreased. In contrast, the conversion rate has increased slightly.

The results of ultrasonographically-guided needle aspiration in amoebic abscess of the liver were presented by Pham Van *et al.*[9] from Hué, Vietnam. Of 1512 patients hospitalized from 1990 to 1995 for an amoebic abscess of the liver, 1289 (85 per cent) were treated by this approach. Abscesses of less than 40 mm (9 per cent) were treated medically without needle aspiration and those of more than 170 mm (1 per cent) or with peritonitis (5 per cent) were operated on. Treatment with metronidazole or dehydroemetin was used in all cases. A second aspiration was necessary in 25 per cent of the patients and a third aspiration in 10 per cent. Three complications were observed, two haemorrhages and one fistula. There was no postprocedure death. Nine patients had a recurrent abscess after discharge from hospital. Results were considered as good in 1273 patients (99 per cent). The authors suggest that in amoebic abscess of the liver with a diameter between 40 and 170 mm, ultrasonographically-guided needle aspiration associated with amoebicidal treatment may be the standard therapy.

Cardiac surgery

A consecutive series of 110 patients, below 60 years of age, operated on between July 1984 and December 1993, were reported by Aupart *et al.*[10] from Tours. These patients underwent aortic valve replacement with a Carpentier–Edwards pericardial valve. Mean clinical status was 2·25 There were no operative deaths. All but three patients were followed for a mean of 4·8 years. The 10-year actuarial survival rate was 91 per cent. Eight valve-related complications (7 per cent) were observed: three cases of endocarditis, three of structural failure, one thromboembolic event and one perivalvular leak. One patient died from a valve-related cause and two required reoperation. The 8-year actuarial probability of absence of valve-related death was 99 per cent, of thromboembolism 98 per cent, of endocarditis 96 per cent, of reoperation 96 per cent and of valve failure 97 per cent. The authors concluded that the 10-year valve-related complication rate is satisfactory for young patients, but the later durability of the prosthesis remains unknown.

The long-term outcome of a series of 112 patients operated on for aortic stenosis was studied by Eker *et al.*[11] from Lyon. There were 67 men; 68 patients (61 per cent) were in New York Heart Association (NYHA) III and 44 in NYHA IV. There were eight early deaths, six for cardiac reasons. The late mortality rate was 28 per cent. Actuarial survival rate (including postoperative mortality) was 88·5 per cent at 1 year, 77·5 per cent at 5 years, 68 per cent at 10 years and 65 per cent at 15 years. For the authors, results were significantly correlated to a left branch block on preoperative electrocardiography, episodes of complete heart failure, significant coronary stenosis or coronary bypass and the type of cardioplegia.

In a series from Lille[12], 36 patients underwent surgical treatment for intractable ventricular tachyarrhythmias after myocardial infarction between December 1986 and December 1994. The inducibility of sustained monomorphic ventricular tachycardia and its resistance to antiarrhythmic drugs were confirmed in all patients by preoperative electrophysiological studies. The patients were divided into two groups (I and II) according to non-guided or guided intraoperative cardiac mapping. In group I, 22 non-guided surgical procedures were performed. In subgroup A, 17 patients underwent encircling thermic exclusion by neodymium yttrium–aluminium–garnet laser beam and another five (subgroup B) had extended cryoablation with endocardial resection. Mean preoperative left ventricular function in subgroups A and B was 35 and 30 per cent respectively. Ten coronary bypasses (eight in subgroup A and two in subgroup B) and one mitral valve replacement (subgroup A) were also performed. The perioperative mortality rate was 6 per cent (one of 17) in subgroup A. No deaths occurred in subgroup B. Ventricular tachycardia recurred spontaneously in two patients (subgroup A) and seven remained inducible after evaluation by electrophysiological studies. In group II, 14 patients underwent extended cryoablation guided by intraoperative cardiac mapping including endocardial resection in all cases. The mean preoperative left ventricular function was 33 per cent. Mitral valve replacement was achieved in two patients. One perioperative death occurred. Clinical recurrence of ventricular tachycardia occurred in one patient and two remained inducible after electrophysiological studies. Grandmougin *et al.* concluded that the better results obtained in group II may be explained by available detection and destruction of deep septal arrythmogenic substrates and the authors recommended this technical procedure.

Two cases of an unusual complication, right ventricular free wall rupture secondary to mediastinitis, after cardiac surgery were reported by Valla *et al.*[13]. This complication is characterized by the singular mechanism of rupture (traction involving the right ventricular free wall and chest adhesion) which occurs during episodes of coughing. Treatment by omentoplasty ensured a favourable outcome in both cases.

D. Castaing

Annales de Chirurgie
31 Boulevard de Latour-Maubourg
75007 Paris
France

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British Journal of Surgery 1996, 83, 1694–1696

Der Chirurg
Zeitschrift für alle Gebiete der operativen Medizin
Organ des Berufsverbandes der Deutschen Chirurgen e.V
Organ der Deutschen Gesellschaft für Chirurgie

Digest

For this quarter's digest Professor Christian Herfarth and Dr Thomas Lehnert have selected the best from the April to June 1996 issues of *Der Chirurg*. A digest of the *BJS* for the same period, written by Mr Colin Johnson, appears in the German journal.

Reviews

Surgical procedures aimed at correction of functional deficits of the anorectum are reviewed in a series of articles in the May issue of the journal. Treatment strategies for rectal prolapse are discussed with particular reference to the overall physical status of the often elderly patients[1]. For frail patients the authors prefer extra-abdominal rectal resection according to Delorme, which can be performed under spinal anaesthesia, although functional outcome results in some degree of persisting incontinence and recurrence rates are high. For younger or physically fit patients the transabdominal approach is preferred. Specifically, the authors recommend anterior or posterior rectopexy in combination with sigmoid resection, since these procedures are more reliable in terms of recurrence rates and correction of incontinence. Laparoscopic techniques have also been used for rectopexy and sigmoid resection by the authors. In 11 patients no perioperative complications were noted and patients recovered earlier than a historical group of 58 patients treated by conventional open operation. The authors speculate that the laparoscopic technique may therefore be suitable for old patients and allow for transabdominal operations whereas the transrectal route has been chosen in the past.

Diagnostic investigations and treatment options for primary anal sphincter insufficiency are reviewed by Athanasiadis[2]. The need for a detailed history of the patient, clinical examination, diligent functional tests including anal sphincter manometry, anorectal perception, evacuation proctography, electromyographic mapping, neurophysiological studies (mm. externus and puborectalis) and anal ultrasonography is emphasized. These tests should help to distinguish myogenic from neurogenic lesions and select the most promising technique for repair. The traditional postanal repair has not been completely satisfactory in the hands of the author. Prompted by his personal experience and by a review of the literature, anterior levatorplasty was performed in 54 patients. At a follow-up of up to 5·5 years, 70 per cent of patients had achieved good continence for liquid and solid stool. Warning period, soiling and discrimination were all improved and manometric studies confirmed improved resting and squeeze pressures.

Treatment options for secondary sphincter insufficiency as a result of trauma or iatrogenic injury are reviewed by a Swiss group from Zurich[3]. In their experience overlapping sphincter reconstruction is the treatment of choice for secondary incontinence due to trauma. The technique of this reconstruction is presented in detail. If it fails repeatedly or if more than 50 per cent of the sphincter is destroyed then gracilis myoplasty is indicated. The most frequent cause of secondary sphincter insufficiency in 47 patients (median age 47 years) treated by overlapping sphincter reconstruction was fistulectomy, followed by perineal tears. Early continence rates at 30 days after operation were 82 per cent for good-to-excellent function, but this deteriorated to only 70 per cent towards the end of the follow-up period. Better overall results were obtained in patients with sphincter insufficiency following perineal tears (81 per cent good-to-excellent results) than in patients with incontinence after fistula surgery (64 per cent).

Laparoscopy

In a prospective randomized trial from Austria[4] open and laparoscopic appendicectomy were compared in 169 patients. Eighty-seven patients were randomized to laparoscopy and 82 had conventional appendicectomy. Both groups were comparable regarding sex, age, Broca and American Society of Anesthesiologists (ASA) scores, pathology of the appendix and previous operations, although the conventional operation was performed more often by surgeons in training than the laparoscopic technique (66 *versus* 48 per cent). Median operating times were 35 min for the laparoscopic and 31 min for the open procedure. No patient required conversion from laparoscopy to open surgery. Wound infection rates were 7 per cent for laparoscopy and 10 per cent for conventional operation. Hospital stay, wound discomfort and return to sports activities were all significantly in favour of laparoscopic appendicectomy, although the authors noted that laparoscopically treated patients resumed sport activities before they returned to work. No difference was noted regarding return to work (14 *versus* 16 days after operation) and cosmetic results. The authors conclude that conventional and laparoscopic appendicectomy are largely equivalent, but the latter may be advantageous in grossly obese patients and if pathology other than appendicitis cannot be excluded.

Recurrent inguinal hernia repair

Inguinal hernia repair is still one of the most common surgical conditions. It has received renewed interest since the advent of laparoscopic techniques and the development of minimally invasive preperitoneal mesh repair procedures. In addition a number of open techniques for preperitoneal mesh reinforcement have been reported in recent years. Schumpelick and Arlt[5] from Aachen have adopted transinguinal preperitoneal mesh prosthesis for repair of inguinal and femoral hernias. This technique was predominantly used in older patients with recurrent hernia or large primary hernia when the transverse fascia was not suitable for tension-free Shouldice repair. During 1994 and 1995 a total of 689 patients with inguinal or femoral hernia were treated. In 58 patients with primary ($n = 4$) and recurrent ($n = 54$) hernia a preperitoneal Marlex mesh (C. R. Bard, Billerica, Massachusetts, USA) was implanted. All patients had a fascial defect greater than 3 cm. The hernia sac was dissected free and the posterior wall of the inguinal canal was exposed. The transverse fascia was opened and separated from the preperitoneal fat. The inferior epigastric vessels were divided if they hindered mesh placement. Dissection was continued to expose Cooper's ligament and allow at least 5 cm circumferential placement of Marlex mesh. The mesh was incised to allow accommodation of the spermatic cord and closed again laterally with non-absorbable sutures. Distally it was fixed to Cooper's ligament and proximally advanced preperitoneally to be secured to the externus oblique aponeurosis. The posterior wall of the inguinal canal was closed over the mesh according to Bassini or Shouldice. Using this method one patient required needle evacuation of a haematoma and another patient had a subcutaneous infection without infection of the prosthetic graft. Twenty-six of 58 patients were operated under local anaesthesia. Operating time was approximately 60 min for recurrent hernia. Routine sonographic studies indicated seroma formation until day 10 after operation, but this did not require intervention. Postoperative mobilization, analgesic use and hospital stay were the same as for conventional Shouldice repair. Follow-up examinations 3–24 months after operation did not reveal recurrent hernia, late abscess or femoral vessel thrombosis. The authors conclude that transinguinal preperitoneal mesh repair is the appropriate technique for inguinal hernia at high risk for recurrence.

The technique originally described by Stoppa was used[6] by a group from Basel, Switzerland for repair of primary and recurrent inguinal hernia. Between 1989 and 1994, 58 operations were performed in 55 patients with a mean age of 65 years. Some 79 per cent of the patients had unilateral and 21 per cent bilateral inguinal hernia. Fifty-six operations were performed for recurrent hernia. Mean(s.d.) duration of operation was 74(21) min. One patient required operative evacuation of a haematoma; there were no infections and no deaths. Follow-up was complete for all 55 patients and ranged from 12 to 76 months with a mean(s.d.) follow-up of 35(18) months. Ten patients complained of intermittent or persistent pain and eight had atrophy of the testicle. Eight of 55 patients had developed recurrent inguinal hernia. Review of the operative notes indicated that the implanted mesh probably was too small in five patients. The authors relate their results to a review of the literature and conclude that Stoppa's technique is a successful method for the treatment of recurrent inguinal hernia.

Oesophageal cancer

Long-term prognosis of oesophageal carcinoma is usually poor; this has been related to late diagnosis of the disease. Very limited experience has been accumulated in Western countries with early stage cancer of the oesophagus. Hölscher and colleagues[7] from Munich have therefore evaluated their experience with early (T_1) squamous cell carcinoma of the oesophagus. Between 1982 and 1995 a total of 65 patients with squamous cell cancer limited to the mucosa ($n = 17$) or infiltrating the submucosa ($n = 48$) were treated (median age 54 (range 36–73) years). This excluded patients with yT_1 tumours following preoperative radiochemotherapy. Patients with carcinoma distal to the tracheal bifurcation were generally treated by two-field lymphadenectomy, while three-field lymphadenectomy was performed for tumours of the upper thoracic or cervical oesophagus. Postoperative complications were recorded in 49 per cent of patients and the in-hospital mortality rate was 11 per cent. Pathohistological examination indicated that resection was complete (R_0) in 92 per cent of patients, while three patients were considered to have had R_1 resection and two R_2 (one for distant metastases and another for concomitant metastatic cancer of the pancreas). Ten patients had multicentric disease in the oesophagus. The mean number of lymph nodes removed was 23 (range 13–39) and 11 of 65 patients had lymph node metastases; all these patients had tumours infiltrating the submucosa. All 17 patients with mucosal tumours were node negative. Follow-up was complete for all patients and ranged from 0·5 to 12·6 (median 4·5) years. The overall 5-year survival rate was 62 per cent for curatively resected patients ($n = 60$) irrespective of the depth of infiltration of the primary tumour. The presence or absence of lymph node metastasis was a major prognostic factor with 71 per cent 5-year survival for node-negative patients and 33 per cent survival for node-positive patients. The paper is completed by a review of the pertinent literature, which confirms that early diagnosis of oesophageal cancer is critical for good long-term prognosis.

Colorectal carcinoma

Preoperative radiotherapy is now widely used for advanced rectal carcinoma. Critics hold that adjuvant radiotherapy may only delay recurrence, but would not increase long-term survival rates beyond 5 years. In a comparative non-randomized study from Springfield, Massachusetts, 149 patients undergoing surgery for rectal cancer between 1972 and 1979 were re-examined to determine long-term effects of preoperative radiotherapy[8]. Of the 149 patients with resectable carcinoma, 40 were treated with 40–45 Gy external beam ^{60}Co radiotherapy using the opposite field technique. Some 34 of 40 patients in the radiotherapy group and 89 (82 per cent) of 109 treated by operation alone had complete tumour resection and a known tumour status at 10 years' follow-up. Five patients were lost to follow-up. After a median follow up of 125 months, survival of the irradiated patients was significantly better than that of controls (77 *versus* 57 per cent at 5 years and 74 *versus* 41 per cent at 10 years; $P = 0·004$). Disease-free survival of patients whose resection margins were free was also superior for the irradiated group (85 *versus* 59 per cent at 5 years and 80 *versus* 45 per cent at 10 years; $P = 0·004$). The effect of preoperative radiotherapy on survival and recurrence-free survival was still demonstrable when multivariate analysis accounted for stage of the disease. The authors conclude that the survival advantage for 40–45 Gy preoperative radiotherapy in the treatment of rectal cancer persists after 10 years of follow-up.

Ch. Herfarth
Editor
Th. Lehnert
Assistant to the Editor

Der Chirurg
Chirurgische Universitätsklinik
Kirschnerstrasse 1
D-69120 Heidelberg
Germany

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British Journal of Surgery 1996, 83, 1697–1701

Laparoscopic fenestration in polycystic liver disease

M. KABBEJ, A. SAUVANET, D. CHAUVEAU*, O. FARGES and J. BELGHITI

*Department of Digestive Surgery, Hôpital Beaujon, Clichy and *Department of Nephrology, Hôpital Necker, Paris, France*
Correspondence to: Professor J. Belghiti, Department of Digestive Surgery, Hôpital Beaujon, 100 Boulevard du Général Leclerc, 92118 Clichy, France

Sixteen laparoscopic cyst fenestrations for symptomatic adult polycystic liver disease (APLD) were performed in 13 women, including four patients who had had previous attempts at treatment (percutaneous sclerotherapy in two and fenestration via a laparotomy in two). The median number of cysts deroofed was 32 (range 18–58) during the 13 primary procedures. There was no inhospital death. Postoperative transient ascites occurred in six patients. After operation 11 patients experienced immediate relief of symptoms but during a median follow-up of 26 (range 6–49) months, eight of these patients developed recurrent symptoms. Two patients underwent three repeat laparoscopic fenestrations, at which time perihepatic adhesions were rare and no complication occurred. Because repeat procedures may be performed, laparoscopic fenestration appears to be useful for the treatment of symptomatic APLD. However, it is less effective than fenestration at open surgery or liver resection and should be employed only in patients with predominantly large cysts.

Adult polycystic liver disease (APLD) is a rare condition that usually occurs in association with polycystic kidney disease[1–4]. Although APLD is rarely symptomatic, some patients develop incapacitating symptoms or complications. In these patients, various treatments have been advocated, such as percutaneous sclerotherapy, fenestration, hepatic resection and even liver transplantation[1–4]. Of these, fenestration is the most widely used and consists of the deroofing of the cysts, starting with the most superficial ones and, stepwise, opening the deeper ones[2,5,6]. There is, however, a risk of symptomatic recurrence in patients whose cysts have been deroofed incompletely; in these patients, repeat fenestration appears to be technically more difficult because of the development of tight adhesions at the level of the previously deroofed cysts, and is associated with a less favourable outcome[4,7,8]. Laparoscopic fenestration has recently been described as a safe and effective alternative to fenestration at open surgery in patients with solitary cysts[9,10]. The advantages of the laparoscopic approach include minimal surgical trauma, rapid postoperative recovery and reduced postoperative adhesions, thus allowing repeat procedures to be performed if necessary. The aim of this paper is to report experience of laparoscopic fenestration in patients with APLD, with special reference to long-term outcome and the ability to perform repeat procedures.

Patients and methods

Between January 1991 and July 1994, 15 women were referred with symptomatic APLD. Of these, 13 patients of median age 49 (range 39–61) years underwent 16 elective laparoscopic fenestrations. The other two patients were not selected for the procedure; one with severe kidney failure and untractable ascites underwent combined renal and liver transplantation and the other, whose cysts were predominantly located in the left lobe, had left hepatectomy. The 13 patients undergoing laparoscopic fenestration had incapacitating right upper quadrant or epigastric pain, abdominal discomfort and hepatomegaly at the time of operation. In addition, four patients had dyspepsia resulting from gastroduodenal compression and two had dyspnoea because of pressure on the diaphragm. All these patients had involvement of both liver lobes.

Preoperative investigation included liver function tests, abdominal ultrasonography and computed tomography (CT). The prothrombin time was normal in all patients, serum γ-glutamyl transferase levels were increased in nine (1·5–7 times the normal upper range) and serum alkaline phosphatase levels were raised in five (1·5–2 times the normal upper range). Ultrasonography and CT were used before operation to delineate the distribution of the cysts and served as a reference with which postoperative CT scans were compared. Predominantly large cysts, defined as the presence of at least 15 cysts measuring 5 cm or more in diameter, were encountered in five patients. Polycystic kidney disease was present in all patients, including two with renal insufficiency (serum creatinine concentration range 120–200 μmol/l) and anaemia. Five patients had a family history of adult polycystic kidney disease and six had relatives with APLD. Four patients had had a previous attempt at treatment including percutaneous cyst alcohol sclerotherapy in two and open-surgery fenestration in two, associated in one with left lateral hepatectomy.

Laparoscopic fenestration was performed under controlled ventilation with intraoperative monitoring of body temperature and end-tidal pressure of carbon dioxide. The pneumoperitoneum was insufflated through a Palmer's needle introduced in the left lower quadrant or by open laparoscopy in patients who had undergone previous surgery. Insufflation was controlled to maintain intraperitoneal pressure below 12 mmHg. The laparoscope was introduced via a midline incision made at least 5 cm under the lower margin of the liver, and three additional trocars were inserted, in each flank and near the xiphoid respectively. Fenestration was performed as described previously by Lin *et al.*[2]; in brief, as many cysts as possible were deroofed, starting with the most superficial ones and progressing stepwise into the deeper ones, using scissors and diathermy. When required by the cyst location, the liver was partially rolled either to the right or to the left after sectioning the triangular ligaments. Because it was occasionally difficult to differentiate a cyst wall from an intrahepatic vascular or biliary radicle, deep cysts were punctured before deroofing. Cyst walls were sampled for routine pathological analysis.

Closed suction abdominal drainage was used only in the first seven patients. Trocar orifices were closed by both fascia and skin sutures. All patients received perioperative antibiotics. Presence and duration of postoperative ascites was documented either clinically or by monitoring the fluid output in patients with peritoneal drainage.

Paper accepted 10 April 1996

Results

The median duration of laparoscopic fenestration was 190 (range 95–330) min. The median number of deroofed cysts was 32 (range 18–58) and the median volume of cystic fluid collected was 1·8 (range 0·7–4·6) litres. Fenestrated cysts were located in all liver segments, although access to segments I and VII was usually particularly difficult. In the patient treated previously by resection of segments II and III, the remaining cysts that were located predominantly in segment IV were easily deroofed.

Intraoperative complications occurred in five patients and included hypothermia lower than 34°C (two patients), cardiac failure (one), hypercapnia with respiratory acidosis (one) and injury to the portal pedicle of segment III that was controlled laparoscopically by application of vascular clips (one). None of these complications required conversion to laparotomy; however, laparoscopic fenestration had to be discontinued prematurely in the two patients who developed cardiac failure and respiratory acidosis. Three patients required perioperative transfusion of 3, 3 and 6 units of red cells respectively. Two of them had had preoperative anaemia secondary to renal insufficiency.

There was no postoperative death. Six patients had an uncomplicated postoperative course. Early complications included ascites, pleural effusion and mild renal failure. Postoperative ascites occurred in six patients, including one of the two with pre-existing renal insufficiency. Ascites was bile stained in two patients; one of these patients, in whom closed suction drainage had been instituted during operation, developed infected ascites (*Staphylococcus aureus*). All patients with ascites were treated conservatively by fluid restriction, administration of diuretics and paracentesis, and ascites resolved after a median of 4 (range 1–12) weeks. Right pleural effusion was observed in one patient and resolved spontaneously. Both patients with preoperative kidney failure experienced a transient deterioration in kidney function (evidenced by a rise in serum creatinine levels above 200 μmol/l). Median duration of postoperative hospital stay was 11 (range 3–30) days.

After laparoscopic fenestration, preoperative symptoms initially resolved completely in 11 patients, but persisted in two (patient nos 4 and 13) (*Table 1*). Repeat laparoscopic fenestration was attempted 6 months later in patient no. 4. Patient no. 13, in whom the laparoscopic fenestration had to be discontinued prematurely because of cardiac failure, had small cysts and was in poor general condition with malnutrition and renal failure; for these reasons, repeat fenestration was not considered and this patient was placed on the liver transplant list. Follow-up of the 11 patients who had initial improvement has ranged from 6 to 49 (median 26) months. Symptoms recurred in eight of the 11 patients 6–24 months after the initial laparoscopic fenestration. In three patients with predominantly large cysts, the onset of symptom recurrence was delayed for 18–24 months, and in the remaining five symptoms recurred within 18 months of operation. Of the eight patients with recurrent symptoms, five with mild symptoms were not reoperated on whereas the other three patients (nos 1, 7 and 12) had four repeat fenestrations.

Overall, four patients had reoperation for symptomatic recurrent symptoms. Two patients underwent repeat laparoscopic fenestration. A repeat fenestration was attempted 6 months after the initial procedure in patient no. 4, but the procedure was ineffective and the patient was subsequently lost to follow-up. In this patient multiple small cysts all around the liver clearly impeded the efficiency of fenestration (*Figs 1* and *2*). Patient no. 1 was reoperated on twice, 24 and 43 months respectively after the initial laparoscopic fenestration. In this patient, recurrence was attributed to the growth of previously untreated cysts and each fenestration was followed by an immediate relief of symptoms; the presence of large cysts probably increased the effectiveness of fenestration (*Figs 3* and *4*). The duration of these three repeat laparoscopic fenestrations were 120, 210 and 330 min respectively. The postoperative course was uncomplicated (except for a single episode of

Table 1 Results of laparoscopic fenestration in 13 patients with symptomatic polycystic liver disease

Patient no.	Previous treatment	Predominantly large cysts	Immediate relief of symptoms	Length of follow-up (months)	Evaluation at last follow-up	Repeat laparoscopic fenestration (months)	Reoperation via laparotomy
1	None	+	+	49	No symptoms	24 and 43	
2	None	+	+	45	No symptoms		
3	None	−	+	39	Mild symptoms		
4	Sclerotherapy	−	−	18	Severe symptoms	6	
5	None	+	+	26	Mild symptoms		
6	None	+	+	26	Mild symptoms		
7	None	−	+	26	No symptoms*		Fenestration at 25 months
8	Fenestration	−	+	16	Mild symptoms		
9	None	+	+	9	No symptoms		
10	Lobectomy and fenestration	−	+	9	No symptoms		
11	None	−	+	10	Mild symptoms		
12	Sclerotherapy	−	+	6	No symptoms*		Lobectomy and fenestration at 6 months
13	None	−	−	3	Severe symptoms		

*Complete return of symptoms before reoperation via laparotomy

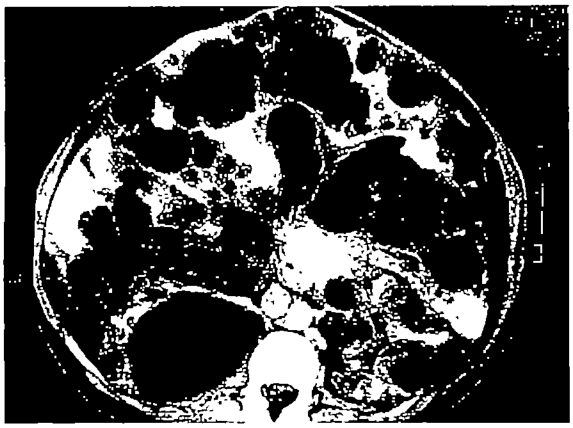

Fig. 1 Preoperative computed tomogram of patient no. 4. The cysts are less than 5 cm in diameter. Note the multiple thin-walled cysts located anterior to the stomach and the right kidney

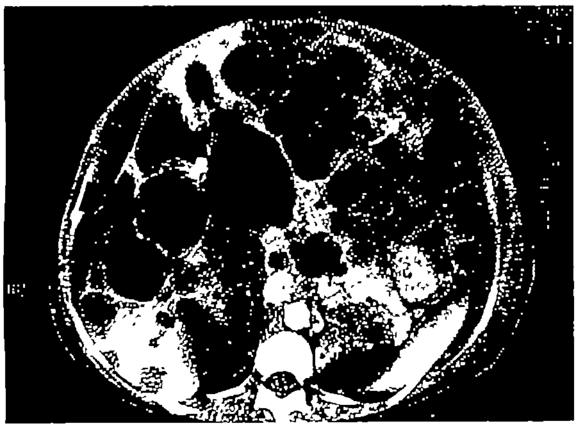

Fig. 2 Computed tomogram of patient no. 4 three weeks after laparoscopic fenestration. Note the fenestrated superficial cyst of the right lobe (arrow), the non-fenestrated intrahepatic cysts and perihepatic ascites

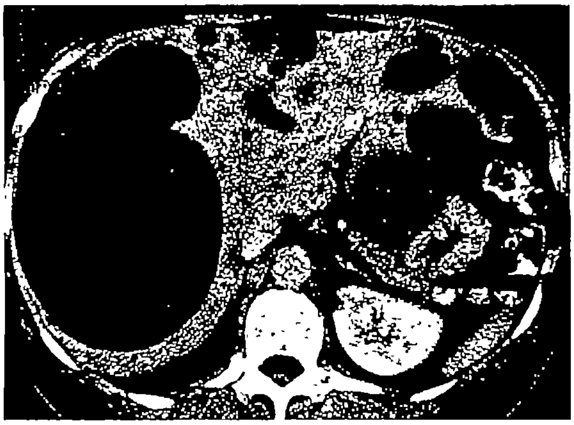

Fig. 3 Preoperative computed tomogram of patient no. 1. The largest cysts are located in the right lobe and the intracystic walls are seldom

transient ascites) in each case and no patient required blood transfusion.

The other two patients underwent laparotomy. Patient no. 7 had diffuse small cysts; laparotomy was considered because of the poor result of the repeat laparoscopic fenestration observed in patient no. 4. Patient no. 12 had cysts located mainly in the left lobe, and therefore underwent left lobectomy associated with fenestration of cysts located in the right lobe.

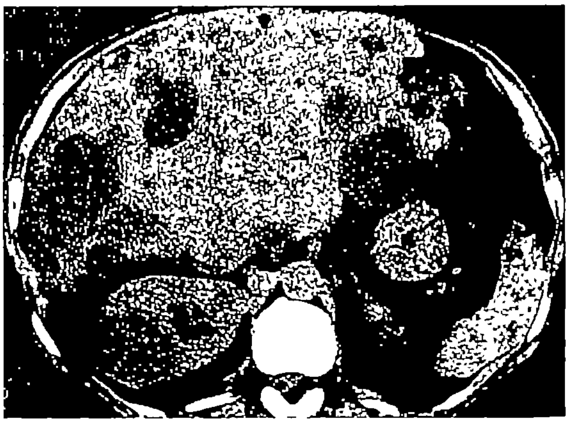

Fig. 4 Computed tomogram of patient no. 1 three months after the third laparoscopic fenestration Note the decrease in size of the liver with ascent of the right kidney

At the time of these five reoperations (patient nos 1, 4, 7 and 12), adhesions around the previously fenestrated cysts were rare except in the infrahepatic area, where the greater omentum had to be separated from the liver.

Discussion

APLD is a rare disorder usually associated with autosomal dominant polycystic kidney disease, with an increasing prevalence associated with age and female sex[3,11,12]. It is usually asymptomatic[3,11,12]. Abdominal pain, dyspepsia and dyspnoea may be observed in patients with massive hepatomegaly[5,12]. Complications of APLD such as ascites, oesophageal varices, jaundice and hepatic failure, are rare[13–16]. A variety of treatments have been advocated for symptomatic APLD, ranging from percutaneous aspiration with or without alcohol injection into the cystic cavities[1,5,17] to liver transplantation, indicated either because of hepatic failure or because the size of the liver precludes renal transplantation[4,18].

Cyst fenestration, according to the technique described by Lin *et al.*[2], is the treatment of choice for APLD complicated by pain and/or the effect of pressure on adjacent structures[2,5,6]. However, the success of this procedure is hampered by a relative inability to deroof widely the smallest cysts, and recent studies[6,16] have reported a 23–57 per cent incidence of symptom recurrence. Repeat fenestration is technically difficult because of extensive perihepatic adhesions and may, in addition, complicate liver transplantation, should this be required[4,7,8]. Fenestration combined with resection of the liver segments that are the most involved by the cystic disease seems to have a more favourable long-term outcome but is associated with high mortality and morbidity rates, ranging from 3 to 22 per cent and from 20 to 67 per cent respectively[3,19,20]. Furthermore, incidences of symptomatic recurrence as high as 33 per cent have been reported[19]. In fact, the long-term prognosis of APLD is related mainly to renal failure resulting from associated polycystic kidney disease[11]. For these reasons, it is reasonable to advocate a low-risk therapy for the treatment of liver cysts.

Laparoscopic deroofing has recently been used as an alternative to open surgery in patients with liver cysts[9,10,21]. Because of the drawbacks of all treatments proposed for APLD, and because of the potential advantages of the laparoscopic approach (including rapid recovery and few postoperative adhesions), laparoscopic fenestration was evaluated prospectively for this purpose.

Laparoscopic fenestration was feasible in all patients in this series. Complications related to the laparoscopic approach included hypothermia, hypercapnia and cardiac failure. Hypothermia and hypercapnia are due to the excessive duration of the procedure, necessary because of the large number of cysts to be fenestrated. Hypothermia should be actively prevented by warming both the carbon dioxide used to maintain the pneumoperitoneum and the saline used for peritoneal lavage, as well as by the use of a forced warm air blanket. Hypercapnia with respiratory acidosis can occur during long laparoscopic procedures despite hyperventilation because of the passage of carbon dioxide through the peritoneal wall[22]. The patient who experienced intraoperative cardiac failure had huge hepatomegaly. As chronic venous outflow obstruction related to extrinsic compression of the hepatic veins and the inferior vena cava by hepatic cysts has been documented previously in massive APLD[23], the impaired cardiac function in this patient was attributed to caval compression by both hepatomegaly and pneumoperitoneum. The laparoscopic approach does not seem to improve the tolerance of fenestration in patients with renal insufficiency. Mild anaemia before operation contributed to blood requirements in two patients with renal insufficiency and both experienced a transient postoperative increase in serum creatinine level. It should, however, be emphasized that no patient had severe renal failure or required dialysis at the time of the procedure; no conclusions on the safety of laparoscopic fenestration in uraemic patients can therefore be drawn from this study.

The main intraoperative technical difficulty was avoidance of injury to the intrahepatic veins and/or portal radicles during extensive deroofing. These pedicles can occasionally be difficult to differentiate from a cyst wall; cyst wall puncture using a fine needle or laparoscopic ultrasonography may help to reduce the risk of vascular injury[24].

Ascites is the commonest complication following surgical treatment of APLD[5-7,15]. It has been shown that the peritoneum cannot clear peritoneal fluid in excess of 900 ml daily[25]. The high incidence of postoperative ascites after laparoscopic fenestration requires adequate closure of trocar sites to prevent postoperative ascitic leak. In this study, postoperative ascites occurred irrespective of preoperative renal function: all but one patient in whom it was observed had a normal preoperative serum creatinine level, whereas one of the two patients with renal insufficiency did not develop ascites. Treatment of ascites following fenestration is not standardized. In the present study cimetidine or somatostatin analogues were not used, as suggested in previous reports[7,15]. In this small series there were no cases of acute Budd–Chiari syndrome, a severe complication reported after surgical resection of polycystic liver disease[19,26].

In this study, laparoscopic fenestration provided an initial clinical improvement in 11 of 13 patients. The value of laparoscopic fenestration was estimated during surgery by cranial displacement of the lower margin of the liver, which seemed more important in patients with large cysts than in those with small diffuse cystic disease. The former patients are probably better candidates for laparoscopic fenestration than the latter[21]. However, some apparently large cysts may contain intracystic walls that are only faintly visible on CT (*Fig. 1*) and may preclude the effectiveness of simple fenestration. The long-term results were disappointing: symptom relapse occurred in eight of the 11 patients who had initially improved. Only one patient of the six with follow-up exceeding 2 years had long-term symptomatic relief. This high rate of symptomatic recurrence, sometimes occurring within the first postoperative year, suggests that laparoscopic fenestration for APLD is unable to treat as many cysts as open fenestration or resection. Although laparoscopic fenestration was safely repeated in two patients, reoperation should be considered according to the size, number and location of the cysts. Extensive deroofing of small cysts and resection of localized cysts are clear indications for laparotomy. During all reoperations following laparoscopic fenestration, the most remarkable finding was the lack of adhesions in the subphrenic space, and this may be important should liver resection or transplantation ultimately be required[4].

In conclusion, this experience suggests that laparoscopic fenestration cannot be advocated as the treatment of choice in patients with APLD because of the high incidence of delayed symptomatic recurrence. However, some patients with few large cysts can be treated effectively with this approach, which can be repeated and probably does not preclude more aggressive therapy, such as liver resection or transplantation. For these reasons, laparoscopic fenestration appears as a new procedure with selective indications for patients with symptomatic APLD.

Acknowledgements

The authors thank Mrs F. Gantelmo and Mrs S. Roi for assistance in preparing the manuscript.

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British Journal of Surgery 1996, 83, 1702–1705

Effect of previous sclerotherapy on the outcome of gastro-oesophageal devascularization and oesophageal transection in bleeding oesophageal varices

M. K. ALAM, G. S. M. EL-SAYED, A. M. ABDULMAJEED and A. AL-DOHAYAN

Department of Surgery, College of Medicine, Riyadh Medical Complex, PO Box 2925, Riyadh 11 461, Kingdom of Saudi Arabia
Correspondence to: Professor M. K. Alam

This retrospective analysis studied the effect of sclerotherapy on subsequent oesophageal transection in the management of patients with bleeding oesophageal varices and compared the result with that in those who did not receive sclerotherapy as the primary treatment. Fifty patients were treated by gastro-oesophageal devascularization and oesophageal transection for bleeding oesophageal varices over a 4-year period. Twenty-six patients did not receive sclerotherapy (group 1) and 24 received between one and four sessions of sclerotherapy (group 2) before surgery. Oedema and thickness of the lower end of the oesophagus and some adhesions were noted during surgery in patients who had had previous sclerotherapy; however, stapled oesophageal transection and anastomosis could be performed in all these patients. There was no oesophageal leak in any patient, although there was a higher rate of chest complications (nine *versus* six patients) in group 2. Six patients (12 per cent) died (three in each group) during the postoperative period; three had Child grade C disease. It is concluded that the decision to operate to control bleeding varices should be made early. One or two sessions of sclerotherapy before surgery does not increase intraoperative difficulty or the postoperative leak rate following oesophageal transection. The outcome of surgery is directly related to the state of liver reserve (Child grade).

Bleeding oesophageal varices is a life-threatening complication of portal hypertension. The choice of the most satisfactory treatment remains controversial[1,2]. Sclerotherapy is the most widely used primary treatment to control bleeding from oesophageal varices[3]. However, in a small subgroup of patients, when sclerotherapy fails to control bleeding or its recurrence, surgical intervention becomes essential. Gastro-oesophageal devascularization with oesophageal transection (GDOT) has remained the preferred surgical treatment in the authors' hospital for bleeding oesophageal varices[4], but some surgeons are apprehensive to submit patients for sclerotherapy before GDOT for fear of increased intraoperative difficulties and postoperative complications. This prompted an analysis of experience with GDOT in patients who had had previous sclerotherapy, and a comparison of the results with those in patients who did not receive sclerotherapy before surgery. The main objective of this study was to compare the short-term (during the same hospitalization) results and postoperative complications in these two groups of patients.

Patients and methods

The records of patients treated by GDOT for bleeding oesophageal varices during the 4-year period from July 1989 to June 1993 were reviewed retrospectively. All patients were initially admitted to a gastrointestinal bleeding unit, resuscitated and had upper gastrointestinal endoscopy to establish the diagnosis of bleeding oesophageal varices. Haemoglobin estimation, prothrombin time, liver function tests including serum albumin, urea and electrolyte estimation, indirect haemagglutination (IHA) test for bilharzia, and viral hepatitis screening were done on all patients on admission. Ultrasonography of the upper abdomen was carried out when the patient's condition was stable.

The nature of definitive therapy offered was dependent on the admitting surgical team. One group of surgeons offered surgical treatment as the primary treatment after diagnostic endoscopy and a trial of vasopressin infusion and/or balloon tamponade. Surgery was carried out as an emergency if these conservative measures failed to arrest the bleeding. Otherwise patients were operated on electively.

The other group of surgeons (including the authors' team) offered sclerotherapy as the primary treatment. Sclerotherapy was carried out at the time of diagnostic endoscopy using 5 per cent ethanolamine oleate. Surgery was offered only to those who continued to bleed after sclerotherapy or who rebled after initial control.

The operation was performed transabdominally on all patients. Proximal gastric devascularization, splenectomy, devascularization of the distal 5 cm of oesophagus, a stapled (EEA 25 or 28 mm; US Surgical, Norwalk, Connecticut, USA) oesophageal transection within 2·5 cm of the cardia and a Heinek–Mikulicz pyloroplasty were carried out in all patients. The splenic bed was routinely drained by a large tube drain. All patients were given methylene blue to drink on the fourth postoperative day and had a Gastrografin (Schering, Berlin, Germany) swallow study on the fifth day to demonstrate any leak and patency of the anastomosis. Only after a satisfactory study result were patients allowed oral fluid and the drains removed. All patients had an ultrasonographic examination on days 7–10 to detect any collection and to determine the state of the portal vein.

Results

Fifty patients were treated by GDOT during the 4-year period under study. On the basis of treatment received, patients were grouped into a 'no sclerotherapy group' (group 1, $n = 26$) and a 'sclerotherapy group' (group 2, $n = 24$). The majority of patients were men (92 per cent; 23 in each group) and non-Saudi (78 per cent; 19 in group 1, 20 in group 2). The median age was 42 and 39 years in groups 1 and 2 respectively. Bilharzia was the commonest cause of portal hypertension in both groups. The diagnosis of bilharzia was based on the history of infection and treatment, serological study (IHA) and liver biopsy.

Paper accepted 10 February 1996

Table 1 Liver disease

Liver disease	No sclerotherapy (group 1, $n = 26$)	Sclerotherapy (group 2, $n = 24$)
Bilharzia	17	15
Viral hepatitis	2	1
Bilharzia and viral hepatitis	2	3
Undetermined	5	5
Child grade		
A	12	14
B	12	8
C	2	2

Table 1 presents the characteristics of the liver disease in the two groups. Patients in group 2 had received one to four sessions of sclerotherapy before surgery. Twelve patients had had one session, nine had had two, one had had three, and two had had four sessions of sclerotherapy. The interval between the last session of sclerotherapy and surgery varied from a few hours to over 2 years.

Timing of surgery

Bleeding continued despite conservative treatment in 14 of the 26 patients in group 1 (no sclerotherapy). They were operated on as an emergency within 48 h of admission. Others who responded to conservative measures were operated on electively.

In group 2 (sclerotherapy), 11 of the 24 patients were operated on as an emergency; nine had had one session and two had had two sessions of sclerotherapy. They had continued to bleed or rebled early after sclerotherapy. The remaining 13 patients were operated on electively. The reasons for operating on these patients were presence of fundal varices (three patients who had had one session of sclerotherapy) and recurrent bleeding (ten).

Operative difficulty

Oedema, adhesions and a thickened lower oesophagus were found at operation in patients in group 2. Some difficulties due to adhesions were encountered during mobilization of the lower oesophagus in seven patients, five of whom had received two or more sessions of sclerotherapy. The remaining 17 patients in this group had mild oedema that did not create any difficulty in mobilization of the lower oesophagus. Stapled oesophageal transection and anastomosis was possible in all patients, although two (one who had had four sessions of sclerotherapy) required the smaller size (25 mm) of stapler because of a thickened lower oesophagus.

In group 1 one patient had oesophageal perforation during mobilization. This was repaired, but this patient subsequently died from encephalopathy. There was no clinical evidence of oesophageal leak in this patient, although a Gastrografin study could not be performed owing to his poor condition.

Postoperative morbidity (Table 2)

Chest-related complications were the most common in both groups. No patient in either group developed an oesophageal leak. One patient from each group developed a gastric leak as a result of necrosis of the gastric fundus.

Table 2 Postoperative complications

Complication	No sclerotherapy (group 1, $n = 26$)	Sclerotherapy (group 2, $n = 24$)
Chest	6	9
Wound infection	1	3
Gastric leak	1	1
Encephalopathy	1	2
Haemorrhage	1	1
Urinary tract	1	2
Mesenteric ischaemia	1	0
Rebleeding	0	2

Table 3 Cause of death in relation to Child grade

Child grade	No sclerotherapy (group 1, $n = 26$)	Sclerotherapy (group 2, $n = 24$)
A	1 of 12 (haemorrhage from splenic and pancreatic areas)	1 of 14 (gastric leak due to fundal necrosis)
B	1 of 12 (necrosis of upper two-thirds of stomach and peritonitis)	0 of 8
C	1 of 2 (small performation of oesophagus repaired; developed encephalopathy)	2 of 2 (wound infection, dehiscence and encephalopathy in one, re-exploration for haemorrhage and encephalopathy in one)
Total	3	3

Two patients were re-explored for reactionary haemorrhage. One patient in group 1 developed mesenteric venous thrombosis leading to small bowel ischaemia. He recovered completely following bowel resection and anastomosis. Two patients in group 2 had minor rebleeding during the postoperative period, which did not require blood transfusion. Endoscopy was not performed on these patients for fear of disrupting the oesophageal anastomosis.

Mortality (Table 3)

There were six deaths (three in each group); five of these patients were operated on as an emergency. Two patients (one in each group) who developed gastric fundal necrosis and leak underwent reoperation. One of them (group 1) had a gastric resection and oesophagojejunostomy, while the other (group 2) had excision of the necrosed area with gastric repair. Both patients died subsequently from sepsis and multiorgan failure. Two patients died from progressive liver failure; one of them (group 1) had oesophageal perforation repaired during surgery. The remaining two patients, one from each group, who were re-explored for postoperative haemorrhage, died from disseminated intravascular coagulopathy and encephalopathy. There were four patients with Child C disease in the total study population, three of whom died during the postoperative period.

Discussion

Endoscopic injection sclerotherapy has been shown to be highly effective (80 per cent) in controlling acute variceal bleeding[5]. However, other methods of treatment should be considered in patients who fail to respond to sclerotherapy. Surgical rescue may be required in up to 40 per cent of patients[6]. Staple transection of the oesophagus with or without proximal gastric devascularization has been recommended as a salvage procedure in such patients[3,7,8]. The authors favour the use of GDOT. Oesophageal leakage at the transection site is reported to occur in 5–8 per cent of patients[9,10], although no oesophageal transection site leak was reported in an earlier study from the authors' institution[4]. It has been suggested that increased problems may be encountered during oesophageal transection in patients treated by repeated previous sclerotherapy, which may have produced inflammatory changes and thickening of the lower oesophagus and upper stomach[11]. This has not been found to be a major problem in the present series or by others[12].

Twenty-four (48 per cent) of the 50 patients reviewed in this study had received between one and four sessions of sclerotherapy before surgery. The remaining patients, who did not undergo sclerotherapy, were reasonably matched with the sclerotherapy group with regard to age, hepatic pathology and Child grade. The same type of stapler was used for oesophageal transection and anastomosis in both groups of patients. Oedema and variable degrees of adhesion and thickening around the lower oesophagus were observed in patients who had been treated with sclerotherapy. Adhesions were particularly marked in those who had had more than two sessions. Some difficulty in mobilization of the lower oesophagus was observed in seven patients. Thickness of the lower end of the oesophagus resulting from previous sclerotherapy forced the surgeon to use a smaller size stapler (25 mm) in two patients. Otherwise oesophageal transection was carried out in all patients without much difficulty. No oesophageal transection site leak was demonstrated in any patient. However, two patients in this study, one in each group, developed necrosis of the gastric fundus. This unusual complication may have developed as a result of injury during flush ligation of fundal vessels or more extensive devascularization of the greater curvature.

Two patients in the postsclerotherapy group who had minor rebleeding during the postoperative period were not endoscoped for fear of disrupting the anastomosis. They may possibly have bled from staple-line erosion, as has been reported in the literature[13]. The present authors have noted a higher rate of chest complications in postsclerotherapy patients, which is a well documented complication of sclerotherapy[14].

Chaudhary and Aranya[15] reported a much higher oesophageal leak rate (22 per cent) in their patients. They attributed this to previous sclerotherapy which resulted in increased intraoperative difficulties and a higher oesophageal leak rate. The higher incidence of intraoperative difficulty and oesophageal leakage in their series may have been due, as the authors themselves suspected, to the use of ethanol as sclerosant, which possibly produces more fibrosis[15]. In the present patients ethanolamine oleate was used as this has been found to be superior to other sclerosants[16,17]. The other reason for more intraoperative difficulties in the Chaudhary and Aranya series may have been the higher number of sclerotherapy sessions to which patients were subjected before surgery[15]. The present patients had had fewer (one or two) sessions of sclerotherapy before surgery; only three patients had had more than two sessions. The early decision to operate and the type of sclerosant used in the present patients may have been the reason for reduced adhesion formation, fewer intraoperative difficulties and more satisfactory anastomosis.

With the increasing popularity of sclerotherapy as the primary treatment, a greater number of patients coming to surgery will have had previous sclerotherapy. Other series have not reported higher morbidity rates for oesophageal transection in such patients[18,19]. These studies have identified factors such as Child grade, number of blood transfusions[8] and the timing of surgery as directly affecting the final outcome of surgery. The effect of Child grade on the result of surgery was well observed in the present series: half of all deaths were in patients with Child C disease, and three of the four patients with this stage of disease died after operation.

The results of sclerotherapy to fundal varices are reported to be poor[20]. This has been the authors' experience as well. Sclerotherapy is used to arrest acute bleeding if both fundal and oesophageal varices are present. These patients are subsequently offered surgical treatment. Three patients in this study (group 2) were treated in this way.

It is concluded that injection sclerotherapy should be the first line of treatment for bleeding oesophageal varices. No significant increase in intraoperative difficulty or leak rate was observed when such patients were subsequently operated on. Non-responders should be identified early and treated by surgery. Most authorities recommend surgery after two injections have failed to control bleeding[3,5,7,12]. This will not produce significant adhesion or thickness of the lower oesophagus, and should minimize the intraoperative difficulties of oesophageal transection and reduce the subsequent oesophageal leakage rate. Persisting too long with conservative management and sclerotherapy may have a detrimental effect on surgical outcome. The status of liver function is the single most important factor determining the outcome of surgery.

Acknowledgements

The authors are grateful to the consultant surgical staff of Riyadh Medical Complex for permission to study the patients. They also thank Cora Rivera for typing the manuscript.

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British Journal of Surgery 1996, 83, 1706–1708

Short note

Influence of cholecystectomy on bile duct width

L.-E. HAMMARSTRÖM, T. HOLMIN,
A. EBBESEN[*] and H. STRIDBECK[*]

Departments of Surgery and [*]Diagnostic Radiology, Lund University Hospital, S-221 85 Lund, Sweden
Correspondence to: Dr L.-E. Hammarstrom

The results of published prospective studies on changes in bile duct width after cholecystectomy are contradictory and comprise relatively few patients, often after short or medium-term follow-up. The objectives of this prospective long-term follow-up study were to investigate whether bile duct width increased significantly after cholecystectomy and to seek evidence of biliary obstruction in patients with excessively dilated ducts.

Patients and methods

In a prospective study of preoperative infusion cholangiography *versus* peroperative cholangiography at elective cholecystectomy[1], all patients were subjected to infusion cholangiography on the day before surgery. A total of 120 patients was scheduled for follow-up infusion cholangiography, liver function testing and interview 5 years after operation. The study, including investigation at follow-up, was approved by the ethics committee of the University of Lund. Some 93 patients with a mean age of 60·7 (range 28–91) years who did not have choledochotomy or duodenal mobilization at cholecystectomy were eligible for follow-up at 47–101 (mean 62·8) months after surgery.

Infusion cholangiography was carried out, as previously described[1], before operation and at follow-up after about 12 h of fasting. In 1 per cent of patients at preoperative infusion cholangiography[1], but in none at the follow-up investigation, there were mild or moderate side-effects from the technique All cholangiograms were reviewed by one radiologist (A.E.). Values are the diameter of the bile duct as measured to the nearest millimetre by metal calipers on cholangiograms The values should be divided by a factor of 1·3 to attain the actual bile duct width. The diameter of the common hepatic duct (CHD) was measured immediately below the fusion of the hepatic ducts, and that of the common bile duct (CBD) at the site of its greatest diameter.

Continuous variables were analysed with the Mann–Whitney *U* test (two-tailed) using the QuickStat computer program (Sapio, Lund, Sweden). Differences were taken as significant when $P < 0\cdot05$.

Results

The mean diameter of the CBD was greater than that of the CHD at both operation and follow-up, and the width of both the CBD and CHD was greater at follow-up than at the time of operation (*Table 1*). Twelve patients (13 per cent) of mean age 68·3 (range 36–85) years had an increased duct diameter of 4 (actual width 3·1) mm or more at follow-up. They were older than the 81 patients of mean age 59·0 (range 28–91) years ($P = 0\cdot03$) with no or less than a 4-mm increase in duct width.

Table 1 Bile duct diameter at cholecystectomy and follow-up in 93 patients

	Bile duct diameter (mm)	
	CHD	CBD
At cholecystectomy	5·6 (2–12)	6·2 (3–13)[*]
At follow-up	7·1 (2–17)[‡]	7·8 (3–20)[†][‡]

Values are mean (range). CHD, common hepatic duct; CBD, common bile duct. [*]$P = 0\cdot02$, [†]$P = 0\cdot03$ (CBD *versus* CHD); [‡]$P < 0\cdot001$ (follow-up *versus* cholecystectomy) (Mann–Whitney *U* test)

Discussion

The changes in bile duct calibre are relatively small, which makes comparison by different diagnostic means unreliable. The diagnostic method of choice is infusion cholangiography, as the CBD has been found to distend and collapse over a short period of time, emphasizing the potential error of direct cholangiography[2]. The precision of measurement on cholangiograms has been estimated as 0·5 mm, suggesting that a change in width as recorded on the films of 1 mm or more is significant[3,4]. Taking such differences as the minimum for recording a difference might be the reason why few studies have managed to show significant duct dilatation after cholecystectomy. Provided the method of infusion cholangiography is standardized and the measurements are all done by one individual, the suggested measurement error of ±0·5 mm would be similar in all patients and would not influence the validity of the comparison[4]. Moreover, no difference in CBD width has been noted in patients with non-functioning compared with functioning gallbladders[3]. Thus, the authors believe that the results of this study are reliable owing to the study design, number of patients investigated and length of follow-up.

The results of this study and two previous infusion cholangiography studies[3,4] strongly support the opinion that there is a statistically significant compensatory increase in bile duct diameter following cholecystectomy, which cannot be ascribed to the age-dependent enlargement of the CBD of about 0·3 mm per decade of life[3].

There was no evidence of bile duct obstruction (increase in liver enzyme levels, biliary colic and/or cholangitis) in any of the 12 patients with an increase in the actual CBD width of 3 mm or more (values reported elsewhere)[5], which supports the opinion that the indications for invasive diagnostic or therapeutic procedures on the biliary tree should be carefully considered in this category of patients with ‘inexplicably’ wide ducts. These patients were significantly older than those with a lesser increase in duct diameter, suggesting an age-related weakness of the bile duct wall as a cause of excessive dilatation.

Paper accepted 10 February 1996

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Short note

Pneumonia presenting with acute abdominal pain in children

D. RAVICHANDRAN* and D. M. BURGE

*Wessex Regional Centre for Paediatric Surgery and the *University Surgical Unit, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK*
Correspondence to: Mr D. M. Burge

Abdominal pain is a common cause of emergency admission in children. Although often due to appendicitis and other intra-abdominal causes, extra-abdominal conditions, especially pneumonia, can simulate an acute abdominal catastrophe. Accurate and prompt diagnosis is essential, not only to avoid general anaesthesia and a negative laparotomy in the presence of pneumonia but also to start antibiotic therapy early so as to prevent the complications of pneumonia.

Patients, methods and results

Among 1168 children admitted with acute abdominal pain to a paediatric surgical unit between 1986 and 1992, 19 (1·6 per cent) had pneumonia as the sole cause of symptoms (*Table 1*). Thirteen of these patients were referred with a diagnosis of acute appendicitis. In two cases a chest infection was also queried as a secondary diagnosis.

In eight patients the diagnosis was made on admission (within 2 h), mainly from the presence of physical signs on auscultation of the chest (seven patients). In others the diagnostic delay varied from 4 h to 6 days (mean 29 h). The diagnosis was confirmed in all patients by chest radiography. The child in whom the diagnosis was not made for 6 days had chest radiography on admission, which was abnormal, but this was not appreciated by the surgical team. He was discharged with a clinical diagnosis of mesenteric adenitis without treatment and returned with persistent abdominal pain. The correct diagnosis was made on review of the radiographs. One child had a negative laparotomy; preoperative abdominal radiography showed signs of consolidation of the right lung base, but again this was not appreciated by the surgeon.

All abdominal symptoms disappeared in all children following the treatment of pneumonia, and no sequelae were observed as a result of the diagnostic delay.

Paper accepted 28 February 1996

Table 1 Patient details

No. of patients	19
Male	16
Age (years)	
3–5	9
6–12	10
Mean	6·5
Mean duration of symptoms	20·5 h (range 2 h to 4 days)
Symptoms of upper respiratory infection	16
Physical signs of lung infection	8
Respiratory rate on admission (per min)	
≥ 40	2
< 40	17
General practitioner diagnosis	
Acute appendicitis	13
No firm diagnosis	6
Diagnosis of pneumonia	
On admission (< 2 h)	8
Later than 2 h	11
Site of pneumonia	
Right lung	13 (upper lobe 2, middle lobe 6, lower lobe 5)
Left lung	6 (all lower lobe)
Mean (range) white blood cell count ($\times 10^9$/l) ($n = 15$)	19·3 (9·7–29·9)
Blood culture ($n = 14$)	
Positive	1 (*Staphylococcus aureus*)
Negative	13
Laparotomy performed	1

Discussion

It is well known that abdominal pain may be the presenting symptom of pneumonia in children, but the mechanism of this symptom is not clear. The theory of referred pain from irritation of the diaphragmatic pleura is refuted by the findings that pneumonia often affects the upper or middle lobes (41 per cent) and that left-sided pneumonia is associated with right-sided abdominal pain. The pain may arise from a mechanism similar to that of mesenteric adenitis, although the mechanism of that pain is still unclear.

The problems facing the surgeon are the exclusion of an acute intra-abdominal lesion requiring laparotomy and the early diagnosis of pneumonia. The mean diagnostic delay of 29 h is indicative of the diagnostic difficulties encountered, but it was not associated with an increased morbidity rate. Diagnosis of pneumonia was difficult in the absence of lower respiratory signs. A raised respiratory rate in pneumonia has been suggested as useful[1], but tachypnoea can also occur in peritonitis[2] and only two children in the present series had a raised respiratory rate. Blood cultures and white cell counts were also not helpful.

Despite these difficulties, most serious diagnostic errors in this study were avoidable. The negative laparotomy rate in the present study was low (one child) compared with that in other studies[3,4], and in this child consolidation of the right lung base on abdominal radiography was overlooked. Abdominal radiography performed to investigate abdominal pain in children may include lung bases and reveal consolidation or parapneumonic effusions[4,5]. Often, the problem is a failure to look at the lung bases on the radiograph[4]. The recommendation to perform anteroposterior and lateral chest radiography in all children with abdominal pain[3] is unlikely to be heeded as only 2–5 per cent of such children have pneumonia[5], and only 1·6 per cent in this series. However, chest radiography should be performed in a child with abdominal pain of unknown cause, especially if there is pyrexia, an increased white cell count or respiratory symptoms. Given that the radiological features of early pneumonia may be subtle and were missed by the surgical team in two children in this series, it is essential that radiographs are reviewed by an experienced radiologist before being declared normal.

In summary, children with pneumonia and abdominal pain pose a difficult diagnostic problem especially when there are no physical signs of pneumonia. However, with increased vigilance the diagnostic delay and negative laparotomy rate can be reduced.

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British Journal of Surgery 1996, 83, 1709–1711

Intrahepatic segment III cholangiojejunostomy in advanced carcinoma of the gallbladder

V. K. KAPOOR, R. PRADEEP, S. P. HARIBHAKTI, V. SINGH, S. S. SIKORA,
R. SAXENA and S. P. KAUSHIK

Department of Surgical Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226 014, India
Correspondence to: Mr V. K. Kapoor

The majority of patients with advanced carcinoma of the gallbladder have irresectable disease and require palliation for jaundice, pruritus and cholangitis. Intrahepatic segment III cholangiojejunostomy has been described for palliation of high biliary obstruction in these patients. Forty-one patients with stage IV gallbladder cancer underwent intrahepatic segment III cholangiojejunostomy. Subsequent jaundice, pruritus and cholangitis were documented; liver function tests and isotope hepatobiliary scans were performed. All patients had jaundice, 29 had pruritus and 12 had cholangitis. Postoperative complications included anastomotic leak in six patients and wound infection in six. Five patients died within 30 days of operation. Thirty-two patients were available for follow-up. The procedure failed to relieve jaundice, pruritus or cholangitis in four patients; 18 were free of jaundice, pruritus and cholangitis until death or last follow-up, and ten had recurrent jaundice or cholangitis. Isotope scanning was found to be useful to predict success of the procedure. Intrahepatic segment III cholangiojejunostomy provided excellent palliation from jaundice, pruritus and cholangitis with acceptable mortality and morbidity rates in patients with advanced carcinoma of the gallbladder.

Carcinoma of the gallbladder is the commonest biliary tract malignancy. Unfortunately most patients have advanced disease at the time of diagnosis. Jaundice is common, and pruritus and cholangitis are distressing associated features. A large single-centre experience with intrahepatic segment III cholangiojejunostomy for palliation of these symptoms in patients with advanced gallbladder cancer is presented.

Patients and methods

A total of 297 patients with gallbladder carcinoma were seen between 1989 and 1994 in this department. Surgery was performed in 173 patients (58 per cent); biliary–enteric bypass by intrahepatic segment III cholangiojejunostomy was performed in 41 patients (24 per cent) operated on. A further six patients who had segment III bypass and cholecystojejunostomy have been reported elsewhere[1].

Patients were followed until death by hospital visits and/or postal questionnaire. Jaundice, pruritus and cholangitis were documented by clinical evaluation. The duration of time without any of these symptoms was defined as duration of well-being and the comfort index was calculated as the duration of well-being expressed as a percentage of total survival[2]. Liver function tests were performed and radioisotope hepatobiliary scans were obtained with BULIDA or Mebrofenin.

Results

The mean age of the 41 patients who underwent intrahepatic segment III cholangiojejunostomy was 51 (range 30–76) years; 31 were women. All patients had features of advanced gallbladder carcinoma: pain, gallbladder mass, anorexia and weight loss at the time of presentation. All patients had jaundice with mean serum bilirubin concentration of 19·9 (range 4·0–35·2) mg/dl; 29 had pruritus and 12 cholangitis. The diagnosis of gallbladder cancer was confirmed by ultrasonography and fine-needle aspiration cytology. The tumour was Union Internacional Contra la Cancrum–American Joint Committee on Cancer tumour node metastasis stage IV in all patients. At operation, metastases were present in the liver, peritoneum or omentum in ten patients; all others had advanced locoregional disease. Gastrojejunostomy was also performed in 22 patients.

Two patients died in hospital: one from myocardial infarction and arrhythmia, and the other as a result of anastomotic leak and sepsis. Three patients died after discharge from hospital within 30 days of operation: one had liver metastases; another died after a cerebrovascular accident; and the third, who had developed an ascitic leak and upper gastrointestinal bleeding, left the hospital against medical advice and was presumed to have died within 30 days.

Twenty-one patients had postoperative complications; these were managed successfully with conservative measures, except in three patients who required reoperation. Anastomotic leak occurred in six patients. Other complications included wound infection in six patients, ascitic leak in four, myocardial infarction in three and bleeding from the drain site and intestinal obstruction in one patient each. A large number of complications occurred because of the gastrojejunostomy: upper gastrointestinal bleeding, five; gastric atony, two; and stomal obstruction, one.

Median postoperative hospital stay was 10 (range 5–55) days; only four patients stayed in the hospital for more than 2 weeks after the operation.

Four patients did not report for follow-up after discharge from hospital; serum bilirubin level in these patients was greater than 5 mg/dl at the last assessment. Thirty-two patients were available for detailed evaluation. The procedure failed to relieve jaundice ($n = 3$), pruritus ($n = 1$) or cholangitis ($n = 4$) in four patients (comfort index 0). Eighteen patients did not have jaundice, pruritus

Paper accepted 3 March 1996

and cholangitis until death or last follow-up (comfort index 100 per cent). Ten patients had recurrent jaundice (four patients) or cholangitis (seven); median comfort index in seven of these patients was 87 (range 77–90) per cent. Isotope hepatobiliary scanning was performed in 21 patients and was normal in 14 (only one of these had recurrent jaundice) and showed partial obstruction in seven (three of these had recurrent jaundice). Four patients required readmission during follow-up: two patients had gastric outlet obstruction and underwent gastrojejunostomy; one had intestinal obstruction and underwent ileotransverse colostomy, and another had persistent cholangitis which was managed conservatively.

Median survival was 5 (range 1–21) months. Five patients survived less than 3 months after operation; 13 survived for 3–6 months, 11 for 6–12 months and three for more than 12 months.

Discussion

The majority of patients with gallbladder carcinoma have advanced disease at presentation with jaundice, pruritus and cholangitis. Resectional surgery is usually not possible. Palliative procedures are therefore required to improve the quality of life.

Jaundice is present in about 50 per cent and pruritus in about 15 per cent of patients with gallbladder cancer[3]. The cause of obstructive jaundice is a block at the upper end of the bile duct either by direct infiltration of the tumour or by compression by metastatic lymph nodes. Extrahepatic hepaticojejunostomy using the common or the left hepatic duct in such situations may technically not be feasible or may not be desirable as the anastomosis will be too close to the tumour and may soon become blocked as a result of tumour infiltration. Intrahepatic segment III cholangiojejunostomy is therefore advocated in such cases. This approach was originally described by Soupault and Couinaud in 1957[4]; the technique has recently been described in detail by Bismuth and Corlette[5] and by Blumgart and Kelley[6].

Most reports of carcinoma of the gallbladder mention palliative biliary bypass but do not specify the exact operative procedure. In a review of more than 3000 patients with gallbladder cancer who were operated on, Piehler and Crichlow[7] reported that bypass procedures (biliary and/or gastric) were performed in 13 per cent of patients. Chijiwa *et al.*[8] mentioned intrahepatic segment III cholangiojejunostomy in gallbladder carcinoma but the number of patients in whom it was performed was not specified. There are a few other reports of intrahepatic segment III cholangiojejunostomy in the literature but the number of patients with gallbladder cancer was too small (less than ten) to draw any meaningful conclusion[9-13]. Although Bismuth and Corlette[5] and Blumgart and Kelley[6] have reported large series of intrahepatic segment III cholangiojejunostomy, the number of patients with gallbladder carcinoma was not specified. The present series represents a large experience with intrahepatic segment III cholangiojejunostomy in patients with carcinoma of the gallbladder.

The 30-day mortality rate of five of 41 patients was the same as that reported earlier[9-12]. Failure of this procedure to relieve jaundice has been reported in 10–15 per cent of patients[5,9]. This has been attributed to lack of communication between the right and left hepatic ducts. The procedure failed to relieve jaundice, pruritus or cholangitis in four patients. These results may reflect a selection bias as patients in whom ultrasonography showed disconnection between right and left hepatic ducts were excluded. Baer *et al.*[11] have, however, recently reported satisfactory results even in patients with hilar obstruction.

Postoperative morbidity in about one-third of the patients was related to the gastrojejunostomy. The desirability of adding prophylactic gastrojejunostomy to the biliary bypass therefore needs to be evaluated critically. The authors are currently conducting a prospective evaluation of gastric emptying in patients with advanced gallbladder cancer. Most of the complications settled with conservative treatment and reoperation was required in only three of the 41 patients, as reported earlier[11,12]. The median postoperative hospital stay of the present patients was only 10 days, much shorter than the 25 and 19 days reported by Baer *et al.*[11] and Guthrie *et al.*[12].

Radioisotope evaluation of the intrahepatic segment III cholangiojejunostomy at follow-up has not been reported before. It was found to be a simple and safe method for evaluating the patency of the biliary–enteric bypass.

Median survival of patients with advanced gallbladder carcinoma is reported to be less than 6 months[7]; a palliative procedure therefore ought to have low morbidity and mortality rates. Patients should have a short hospital stay and go home without tubes and stents. Repeated hospital admission and interventions should not be required to ensure a good quality of life. In the authors' experience intrahepatic segment III cholangiojejunostomy provides excellent palliation from jaundice, pruritus and cholangitis and is associated with a short hospital stay and acceptable mortality and morbidity rates in patients with advanced irresectable carcinoma of the gallbladder.

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Surgical workshop

Quick and simple distal pancreatectomy using the GIA stapler: report of 35 cases

Y. KAJIYAMA, M. TSURUMARU,
H. UDAGAWA, K. TSUTSUMI,
Y. KINOSHITA and H. AKIYAMA
Department of Surgery, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105, Japan
Correspondence to: Dr Y. Kajiyama

A method for distal pancreatectomy using the multifire GIA-80 stapler (US Surgical, Norwalk, Connecticut, USA) is reported that is quicker, associated with reduced blood loss and a lower incidence of pancreatic fistula than with other instruments such as the TA-55 stapler (Auto Suture, Ascot, UK). When performing total gastrectomy with distal pancreatectomy and splenectomy to complete a wide lymph node dissection in patients with advanced gastric cancer, this method of pancreatectomy can be useful.

Surgical technique

After the pancreatic body and tail have been isolated from the retroperitoneal space, the splenic artery and vein are doubly ligated and divided. A GIA-80 stapler loaded with 4·8-mm staples is introduced across the pancreas. The handles of the GIA stapler are then carefully approximated in an effort not to place the splenic vessels between the stapler and pancreas and not to lacerate the pancreas. The cutting lever of the GIA is then fired, leading to amputation of the distal gland. Both the proximal and distal pancreatic stump are stapled with a staggered double row of non-reactive titanium staples. Ligation of the main pancreatic duct is not necessary, and minor bleeding from the staple line can be controlled easily with compression of the pancreas for a few minutes.

Paper accepted 14 March 1996

Outcome

This technique was used in 35 patients who underwent total gastrectomy with distal pancreatectomy and splenectomy. The frequency with which patients required drainage of a pancreatic fistula for more than 3 weeks was 40 per cent, compared with 61 per cent ($n = 184$) after stapling with the TA stapler ($P = 0·04$); this is similar to the fistula rate of 46 per cent ($n = 175$) with manual pancreatectomy (P not significant).

Discussion

One of the most serious complications of distal pancreatectomy is the development of a pancreatic fistula after operation, which may lead to a subphrenic abscess or lethal arterial bleeding from the splenic artery. To minimize intraoperative blood loss and to prevent pancreatic fistula formation, pancreatectomy with a TA-55 stapler[1] or carbon dioxide laser equipment[2] has been described, but these techniques have not been successful. In the authors' large series these other techniques did not improve the incidence of pancreatic fistula.

In addition, the method described here simplifies and shortens the operation because there is no need for ligation of the main pancreatic duct or additional suturing of the pancreas to approximate the anterior and posterior capsule of the gland. The GIA-80 stapler has a shorter distance between staples and between the staple lines than the TA-55 stapler, and it uses staples of a shorter length and smaller diameter than the TA-55. This may explain the good approximation of the pancreatic capsule and closure of the main pancreatic duct, which results in minimal bleeding from the pancreatic stump and no need for ligation of the pancreatic duct.

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British Journal of Surgery 1996, 83, 1712–1715

Outcome of treatment for distal bile duct cancer

Y. FONG, L. H. BLUMGART, E. LIN, J. G. FORTNER and M. F. BRENNAN

Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10 021, USA
Correspondence to: Dr Y. Fong

All patients with distal bile duct tumours over a 10-year period (October 1983 to December 1993) were identified by means of a prospective database. The medical records of 104 patients were reviewed. Univariate and multivariate analysis for predictors of outcome was performed. Median age of the patients was 65 (range 30–89) years. Patients presented with a clinical picture indistinguishable from that of pancreatic ductal adenocarcinoma. Twenty patients had no surgical treatment and 23 had a diagnostic laparotomy only. Biliary bypass was performed in 16 patients and radical resection was performed in 45 (pancreaticoduodenectomy, 39; bile duct excision, six). Operative mortality occurred in two of 45 patients having radical resection and complications in 17. Resection provided significant survival benefit. By univariate and multivariate analysis, resectability and negative node status ($P < 0.001$) were the only predictors of favourable outcome. Sex, age, preoperative stenting, grade of tumour and bilirubin level did not predict outcome. The 5-year survival rate for radically resected, node-negative tumours was 54 per cent. Surgical resection is effective therapy for distal bile duct tumours. These patients have a better outlook than those having resection of pancreatic adenocarcinoma.

Distal biliary obstruction may be produced by any tumour of the periampullary region. Of these, pancreatic ductal adenocarcinoma, ampullary carcinoma, duodenal carcinoma and distal bile duct carcinoma are the most common. Clinical presentation and therapy are similar for these four tumours, but outcome after resection can be very different. After curative resection of pancreatic adenocarcinoma, the 5-year survival rate is less than 15 per cent[1–8], whereas that for ampullary carcinoma is more likely to approach 50 per cent[9–12]. Because of its rarity there are few data on the outcome of therapy for distal bile duct tumours. The few studies that have described treatment are summarized in *Table 1*. The studies span large intervals in the experience of each institution, the largest report[10] being a collected series from 57 institutions over 25 years. The present report examines the treatment of 104 patients with distal bile duct tumours at a tertiary referral centre in order to define perioperative results as well as predictors of long-term outcome.

Patients and methods

All patients discharged from the Memorial Sloan-Kettering Cancer Center with the diagnosis of distal bile duct cancer for the 10-year interval October 1983 to December 1993 were identified from the Department of Surgery's pancreatic–biliary database. This database has been collected prospectively for all peripancreatic tumours since 1983. A total of 104 patients was identified. Data for these patients were then extracted from the database and verified by review of hospital and office charts, as well as interviews with patients. All tumours that involved the bile duct between the cystic duct and the ampulla of Vater were included.

Data examined included: (1) demographics (including age and sex); (2) presentation; (3) pathology; (4) details of surgical therapy; (5) hospital course including complications; and (6) outcome. Follow-up was by personal contact with the patient, patient's family or attending physician. Surgical mortality included all deaths within 30 days of surgery.

Log rank analysis was performed for univariate analysis of survival[16]. The χ^2 test or Fisher's exact test, where appropriate, was used for other univariate comparisons[17]. Proportional hazards regression was used to incorporate all the explanatory variables in the same model[16]. Statistical analysis was performed with the True Epistat statistical package (Epistat Services, Richardson, Texas, USA). Differences were considered significant at the $P = 0.05$ level.

Results

A total of 104 patients was treated in the 10 years of the study. There were 60 men and 44 women of median age 65 (range 30–89) years. Seventy-nine patients had died at the time of last follow-up; median survival from time of resection was 9·7 (range 0–52) months. Median follow-up of survivors was 28 months.

Paper accepted 10 March 1996

Table 1 Studies of distal bile duct cancer

Reference	Year	Length of study (years)	No. of institutions	No. of patients	No. resected	Operative mortality rate (%)	Median survival (months)	3-year survival rate (%)	5-year survival rate (%)
Warren *et al.*[9]	1975	30	1	—	47	21	—	32	25
Nakase *et al.*[10]	1977	25	57	309	161	22	17	8	5
Tompkins *et al.*[13]	1981	25	1	18	12	8	18	28	28
Alexander *et al.*[14]	1984	13	1	14	14	21	16	20	18
Lerut *et al.*[11]	1984	15	1	—	5	—	11	0	0
Tarazi *et al.*[12]	1986	35	1	—	11	0	—	—	17
Nagorney *et al.*[15]	1993	10	1	39	22	—	24	40	40
Present series	1996	10	1	104	45	4	33	46	27

Jaundice, the most common presenting symptom, occurred in 75 per cent of patients. Weight loss was also common, occurring in one-third. Pruritus or pain was reported in one-quarter; fever (17 per cent), nausea (4 per cent) and diarrhoea (3 per cent) were other presenting symptoms.

Twenty of the patients had irresectable disease and were treated non-surgically. The remaining 84 patients had surgery (*Table 2*); 23 of these had only a diagnostic laparotomy with biopsy. Sixteen had surgical biliary–enteric bypasses for irresectable symptomatic disease. There were 45 resections, consisting of 39 pancreaticoduodenectomies and six common bile duct excisions.

Table 2 Operations for distal bile duct tumours

	n
No surgery	20
Laparotomy, biopsy	23
Bypass	
Choledochojejunostomy	5
Choledochojejunostomy and gastrojejunostomy	5
Gastrojejunostomy	1
Hepaticojejunostomy	4
Hepaticojejunostomy and gastrojejunostomy	1
Total	16
Resection	
Pancreaticoduodenectomy	39
Common bile duct excision	6
Total	45

Median hospital stay was 17 (range 1–82) days for patients who had a resection, whereas that for the 39 who were explored and biopsied or bypassed was 15 (range 4–79) days ($P = 0{\cdot}05$). Perioperative death occurred in two of the 45 patients in the resection group and three of the 39 having no resection. Complications occurred in 17 of the patients undergoing resection, and included intra-abdominal abscess in four and pancreatic fistula in three. In 39 patients having no resection, complications occurred in 12 (*Table 3*).

Late survival was related to treatment. For patients offered no surgical therapy, median survival was 7·1 months (*Table 4*). For those subjected to diagnostic laparotomy only, median survival was 5·7 months. Patients who had a surgical bypass had a median survival of 10·3 months. For any of these patients not treated with potentially curative therapy, the 1-year survival rate was 37 per cent, and there were no 2-year survivors. In patients who had a resection, median survival was 32·9 months and the 5-year survival rate 27 per cent.

By log rank analysis the only parameters predictive of long-term outcome were resectability or node status (*Table 5*). Sex, age, preoperative stenting, bilirubin level, surgical margin and tumour grade did not correlate with outcome. Only one of the six cases with a positive surgical resection margin occurred in a patient who had had local excision of the tumour.

Using sex, age, preoperative bilirubin level and node status as variables, analysis by proportional hazards was performed for patients who had tumour resection. Node status was the only independent predictor of outcome

Table 3 Complications after operation for distal bile duct tumours

	Resection ($n = 45$)	No resection ($n = 39$)
Death	2	3
Complications		
Cholangitis	1	3
Pancreatic fistula	3	2
Gastrointestinal bleed	1	1
Sepsis	4	3
Wound infection	1	1
Pneumonia	0	1
Enterocutaneous fistula	0	1
Abdominal abscess	4	0
Hepatic infarction	1	0
Clostridium difficile colitis	1	0
Myocardial infarct	1	0
Total	17	12
Median (range) hospital stay (days)	17 (1–82)	15 (4–79)

Table 4 Long-term outcome related to treatment

Treatment	No. of patients	Median survival (months)	Survival rate (%)		
			1 year	3 years	5 years
No surgery	20	7·1	36	0	0
Laparotomy, biopsy	23	5·7	37	0	0
Bypass	16	10·3	38	0	0
Resection	45	32·9	79*	46*	27*

*$P < 0{\cdot}00002$ (resection *versus* other treatments, log rank analysis)

Table 5 Univariate analysis for predictors of long-term outcome in patients who had a resection

	No. of patients ($n = 43$)	P*
Sex		
M	30	0·8
F	13	
Age (years)		
< 70	26	0·2
≥ 70	17	
Preoperative biliary stent		
No	28	0·3
Yes	15	
Preoperative bilirubin (mg/dl)		
< 2	18	0·09
≥ 2	25	
Preoperative alkaline phosphatase (U/L)		
< 300	21	0·8
≥ 300	22	
Surgical margin		
Negative	37	0·6
Positive	6	
Node status		
Negative	24	0·00003
Positive	19	
Tumour differentiation		
Well	12	0·1
Moderate	23	
Poor	8	
Tumour histology		
Papillary	14	0·09
Scirrhous	28	
Nodular	1	

Table 6 Proportional hazards analysis for risk of death after resection of distal bile duct tumour

Parameter	*P*	Coefficient (SE)	Relative risk
Sex	0·7	−0·2	0·8
Age	0·7	0·009	1·0
Preoperative bilirubin level	0·5	0·02	1·0
Node status	0·001	1·9	6·7

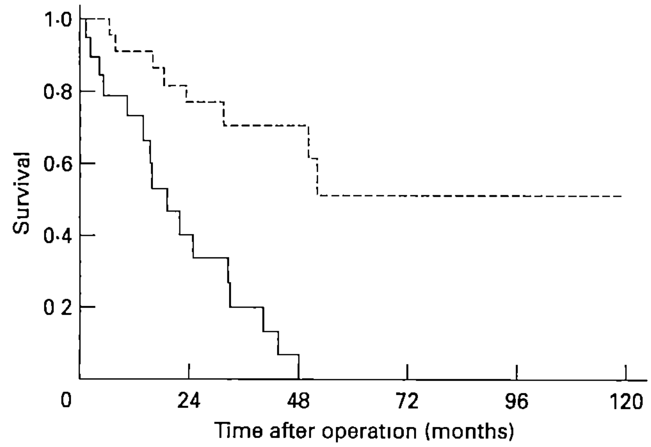

Fig. 1 Effect of lymph node metastasis on outcome after curative resection for distal bile duct cancer. ———, Node positive; ----, node negative

(*Table 6*). Patients with involved nodes had a 6·7 times higher risk of death. Mortality related to node status is illustrated in *Fig. 1*.

Discussion

The rarity of distal bile duct tumours has resulted in a paucity of data. In the authors' prospective database of periampullary cancer, distal bile duct cancer is one-thirteenth as common as pancreatic ductal carcinoma, and represents only 5 per cent of all cancers in the periampullary region. Approximately 24 000 cases of pancreatic ductal carcinoma are found each year[18]; therefore, fewer than 2000 cases of distal bile duct cancer would be expected in the USA each year. Previous data on distal bile duct cancer have been part of a report on either periampullary cancer[9–12] or all bile duct cancers[13–15]. These reports indicate that distal bile duct cancer represents 5–10 per cent of all periampullary cancers, and approximately 20 per cent of all bile duct cancers. The present report confirms that outcome after resection of distal bile duct cancers is different from that for other peripancreatic cancers; the 5-year survival rate following resection of distal bile duct cancer is twice[9–12,13–15] that expected for adenocarcinoma of the pancreas[1–8].

The present study reports a perioperative mortality rate of 4 per cent, identical to previously published experience of resection for pancreatic or ampullary cancer[1]. The exact anatomical origin of the lesion therefore seems to have little influence over the perioperative course. These data are further testimony to the increasing safety of pancreaticoduodenectomy. As recently as two decades ago pancreatic resection was associated with a dismal outcome; operative mortality rates of over 20 per cent were reported[9,10,14,19,20], which led to suggestions that resection was inappropriate and that bypass procedures might perhaps be preferable[19]. Over the past decade the mortality rate associated with pancreatic resection has declined significantly, such that operative mortality rates of less than 5 per cent are reported routinely[1–8]. The present study demonstrates the safety of resection as well as the survival advantage conferred by resection over the alternative of bypass. These data support surgical resection as standard treatment for cancer of the distal common bile duct.

Acknowledgements

This work was supported in part by the Franklin Martin Faculty Fellowship from the American College of Surgeons and the Marilyn Chait Foundation.

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Short note

Biliary papillomatosis

C.-M. LAM, S.-T. YUEN*,
W.-K. YUEN and S.-T. FAN
*Departments of Surgery and *Pathology, University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong*
Correspondence to. Dr C.-M. Lam

Biliary papillomatosis is a rare clinicopathological condition characterized by multiple papillary adenomas involving extensive areas of the biliary tree[1]. The pathophysiology, clinical features and management of this condition are not well understood. Experience of six patients with biliary papillomatosis is reported.

Patients and methods

A re-examination was performed of the histological materials from patients with a reported pathological diagnosis of adenoma or carcinoma of the biliary system, from 1986 to 1994 inclusive. Cases that accorded with the World Health Organization's definition of biliary papillomatosis[1] were analysed.

Results

Six patients with biliary papillomatosis were identified. Their clinical features are summarized in *Table 1*. The mean age was 67 years. Jaundice was the presenting symptom in five patients. One patient had a lesion confined to the gallbladder, and the extrahepatic bile ducts were involved in the other five. Four patients showed additional involvement of the intrahepatic ducts and had microscopic evidence of malignancy. Patient no. 3 had a benign lesion, which progressed to malignancy after 2 years. *Clonorchis sinensis* infestation was observed in patient nos 2 and 4 in whom tiny malignant foci were identified. Excessive mucus secretion from the bile duct was noted in patients 2 and 3 during endoscopic retrograde cholangiopancreatography. In all patients the mucosal surfaces of the biliary tree were found to be replaced by velvety papillary growths. Histological sections showed multiple papillomas covered by epithelial cells with varying degrees of dysplastic change. The mean survival period after surgery was 34 months. Two patients with malignant biliary papillomatosis survived more than 5 years.

Discussion

Biliary papillomatosis is rare. Taguchi *et al.*[2] could identify only 21 cases in the English literature. Malignancy was found in five of them.

The reasons for the high malignancy rate (four of six patients) in the present series may be multifactorial. First,

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Presented in abstract form to the Third Congress of the Asian Society of Hepatobiliary-pancreatic Surgery in Seoul, South Korea, October 1995
Paper accepted 10 February 1996

Table 1 Clinical features of the six patients with biliary papillomatosis

Patient no.	Age	Sex	Clinical features	Localization	Histology	Therapy	History of recurrence	Survival after surgery
1	69	M	Jaundice	Extrahepatic duct	Benign	Pancreaticoduodenectomy	No	12 months (alive)
2	66	M	Jaundice	Extrahepatic duct; recurrence in intrahepatic duct	Malignant	Excision of bile duct, bilateral hepaticojejunostomy	Yes	16 months
3	66	M	Jaundice	Extrahepatic and intrahepatic ducts; abdominal wall and lung metastases	Malignant	Excision of bile duct, extended left hemihepatectomy	Yes	5 years
4	74	M	Jaundice	Extrahepatic duct; recurrence in intrahepatic duct	Malignant	Excision of bile duct, choledochojejunostomy	Yes	86 months (alive)
5	54	F	Epigastric pain	Gallbladder	Benign	Cholecystectomy	No	14 months (alive)
6	73	M	Jaundice	Extrahepatic duct; recurrence in intrahepatic duct	Malignant	Excision of bile duct, bilateral hepaticojejunostomy	Yes	17 months

malignant transformation may not be properly excluded in the 'benign' cases reported in the literature[3]. Second, prolonged follow-up may allow detection of malignant transformation as seen in one of the present patients. This was reported in four other cases with a latent period of 3 months to 6 years[3]. Progression from epithelial dysplasia to carcinoma *in situ* and to frank invasive adenocarcinoma has been suggested[4]. Third, *Clonorchis* infestations may play a contributory role, although this has not been reported previously.

Preoperative diagnosis is usually difficult. The presentation of obstructive jaundice is not specific to biliary papillomatosis. No diagnostic radiological features have been documented. However, the cholangiographic finding of multiple or extensive lesions in the biliary tree may suggest the diagnosis and indicate the extent of papillomatosis. The endoscopic finding of excessive mucus or blood in the duodenal lumen is also supportive, although not diagnostic, of biliary papillomatosis[5].

Surgery remains the primary treatment for biliary papillomatosis. Curettage and drainage of the bile duct have been associated with a high incidence of recurrence. Bile duct resection, pancreaticoduodenectomy and hepatic lobectomy appear to be a logical approach when the involved area can be resected completely. However, even after resection with adequate clear margins, recurrences still occur in the remaining intrahepatic ducts. Nevertheless, the survival rate of the present patients was better than that reported in the literature, where only 20 per cent survived for more than 1 year and only one patient lived longer than 5 years[3].

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British Journal of Surgery 1996, 83, 1717–1721

Complete prevention of impaired anastomotic healing in diabetic rats requires preoperative blood glucose control

M. H. J. VERHOFSTAD and TH. HENDRIKS

Department of Surgery, University Hospital Nijmegen, PO Box 9101, 6500-HB Nijmegen, The Netherlands
Correspondence to: Dr Th. Hendriks

Uncontrolled diabetes severely impairs early healing of experimental intestinal anastomosis. This study aimed to compare the potential beneficial effect of insulin treatment, started before or immediately after surgery. A normal blood glucose level was attained in diabetic rats by twice-daily administration of insulin, commenced either 4 days before operation (insulin-1 group) or on the day of operation (insulin-2 group). A non-diabetic control group and an uncontrolled diabetic group were also studied. Three days after operation, mean(s.d.) bursting pressures in the diabetic group were severely reduced compared with those in controls: 1·0(1·4) *versus* 8·1(2·9) kPa in the ileum and 4·9(4·7) *versus* 18·1(5·8) kPa in the colon. For ileal anastomosis, values in both groups of animals receiving insulin were similar to those in controls, but for colonic anastomosis the mean bursting pressure in the insulin-2 group remained significantly ($P < 0·017$) below that in the insulin-1 group (10·2(6·4) *versus* 20·7(7·9) kPa respectively). After 7 days mean bursting pressures in both ileum and colon were restored to control levels in the insulin-1 group but not in the insulin-2 group. Anastomotic abscess formation after 3 days was also significantly ($P < 0·017$) more common in the diabetic and insulin-2 groups, but not in the insulin-1 group than in the control group. Postoperative blood glucose control alone does not completely prevent the detrimental effects of uncontrolled diabetes on healing intestinal anastomoses.

Wound repair in diabetic patients is frequently beset by complications[1]. This clinical observation has been confirmed in rodents with toxin (streptozotocin)-induced[2–5] and endogenous[6–8] diabetes. The development of cutaneous wound strength is strongly inhibited and associated with reduced accumulation of collagen. It remains to be established whether administration of insulin can return all parameters of wound healing to normal. Model studies in skin indicate that even when the blood sugar level is controlled with insulin, diabetes leads to structurally deficient healing[9], particularly in the early phase after wounding[4].

Impaired healing of intestinal anastomosis will increase the chances of leakage. The assumption that diabetes mellitus should be considered as a factor detrimental to the repair of colonic anastomosis appears well accepted[10,11]. Consequently the presence of diabetes may predispose the surgeon toward a staged procedure rather than construction of a primary anastomosis. In view of these potentially important consequences, there should be reticence in extrapolating results obtained on skin to other soft tissues, such as the gastrointestinal tract[12].

In streptozotocin-induced diabetic rats, anastomotic abscess formation increases and the development of wound strength is severely reduced but, contrary to the situation in skin, this phenomenon is not accompanied by deficient accumulation of collagen[13].

This study reports on attempts to prevent loss of early anastomotic strength by insulin administration. Normoglycaemia was restored either 4 days before operation or from the day of operation onwards.

Materials and methods

Ninety male Wistar rats (mean(s.d.) body-weight 258(15) g) were used in these studies. Rats were randomly divided into four groups: one non-diabetic control group ($n = 20$), one uncontrolled diabetic group ($n = 30$), one diabetic group treated with insulin before and after operation ($n = 20$) and one diabetic group treated with exogenous insulin after operation only ($n = 20$). These groups will be referred to as control, diabetic, insulin-1 and insulin-2 groups respectively. All animals were housed two per cage. They were fed *ad libitum* with standard chow and had free access to water. The animal residence was illuminated from 06.00 to 18.00 hours. All experiments were approved by the Animal Experiments Ethics Review Committee of the Medical Faculty, University of Nijmegen.

The rats in the experimental groups were rendered diabetic by intravenous injection of streptozotocin (Sigma, St Louis, Missouri, USA) in a dose of 50 mg per kg body-weight, freshly dissolved in citrate buffer (0.01 mmol/l, pH 4·5) at a concentration of 12·5 mg/ml. The non-diabetic control group received citrate only.

Three days after injection of streptozotocin, at 18.00 hours, the tail vein blood glucose levels of the rats in the insulin-1 group were measured (Haemoglukotest strips and a Reflolux S reflectance meter; Boehringer Mannheim, Mannheim, Germany). Thereafter, the animals were injected subcutaneously with insulin (heat-treated insulin ultralente bovine 40 units/ml, pH 5.5 (NOVO, Copenhagen, Denmark), dissolved in saline up to a final concentration of 10 units/ml just before use) in a standard dose of 10 units per kg body-weight. On subsequent days insulin was administered twice daily at 09.00 and 18.00 hours, immediately after measurement of tail vein blood glucose concentration. Dosages of insulin were adapted individually for each rat, depending on the actual blood glucose level measured and its body-weight. This regimen was chosen after pilot experiments in which several insulin types, dosages and time schedules were studied (results not shown). Blood glucose levels between 4·0 and 10·0 mmol/l were considered to be normal. The insulin-2 group first received exogenous insulin on the day of surgery at 18.00 hours and animals were subsequently treated in the same way as those in the insulin-1 group. The control group was treated with subcutaneous saline at the same time points that the insulin-1 group received insulin. Tail vein blood from control group animals was also collected twice daily throughout the experiment. The diabetic group was not treated with insulin or saline. Tail vein blood glucose concentration in the diabetic group was measured only at operation and killing.

One week after the streptozotocin (or buffer) injection all rats were operated on by the same surgeon (M.H.J.V.). Animals

Paper accepted 11 February 1996

received an anastomosis in both ileum and colon. Animals from the various groups were operated on alternately. Operations were performed under semisterile conditions using a Zeiss operating microscope. Rats were anaesthetized by intraperitoneal injection of sodium pentobarbital 50 mg/kg A median laparotomy of approximately 4 cm was performed. After resection of a 1-cm control segment, approximately 15 cm oral to the ileocaecal junction, an ileoileal anastomosis was constructed, using eight single-layer inverting interrupted 8/0 Ethilon (Ethicon, Norderstedt, Germany) sutures For the colonic anastomosis a similar procedure was performed, approximately 3 cm oral to the peritoneal reflection. The abdomen was closed with a running 3/0 silk suture for the musculofascial layer and staples for the skin.

One-half of the animals in each group were killed 3 days after surgery and the remaining half after 7 days The abdomen was opened and inspected for signs of infectious complications. The anastomotic segments were resected, leaving surrounding tissue in place, and washed in saline. Faeces were removed carefully Subsequently the anastomotic segment was connected to an infusion pump on one side and to a manometer on the other. Intraluminal pressure was then raised by infusion of methylene blue, dissolved in saline, at a rate of 2 ml/min. Bursting pressure was defined as the maximum intraluminal pressure the segment resisted, expressed in kilopascals. The bursting site was also noted. Differences between groups were analysed for statistical significance with the Wilcoxon rank sum test or a two-tailed Fisher's exact test when appropriate. To correct for the fact that multiple comparisons were made, pairwise comparisons were performed with a level of significance of $\alpha^* = 2\alpha/k$, where k is the number of pairwise comparisons. Thus, differences between groups (six possible comparisons) were considered significant ($\alpha = 0{\cdot}05$) at $P < \alpha^* = 0{\cdot}017$

Results

Mortality

During the study ten rats from the diabetic group died prematurely: two animals died before operation, three during operation and two on the first postoperative day from intestinal volvulus. Three rats died from a ruptured ileal anastomosis, two on day 2 and one on day 6 after operation. Four animals from the insulin-2 group died: three suffered from anastomotic failure in the ileum and subsequent peritonitis within 24 h after operation, while one rat died after the first insulin injection, presumably from hypoglycaemia as the anastomosis was intact. All these animals were excluded from the study. There were no deaths in the control and insulin-1 groups. Mortality in the diabetic group was significantly increased compared with that in control and insulin-1 groups ($P < 0{\cdot}003$, two-tailed Fisher's exact test).

Blood glucose and insulin

Non-fasting blood glucose concentrations in the various 7-day groups are summarized in *Fig 1.* Measurements in the 3-day groups were similar. The rats became hyperglycaemic soon after administration of streptozotocin and developed polyphagia, polydipsia, diarrhoea and polyuria, but no ketoacidosis within the experimental period. Blood glucose levels during uncontrolled diabetes were increased approximately fourfold and remained strongly raised throughout the experiment. Twice-daily administration of insulin resulted in normal blood glucose levels within 2 days of starting treatment. Preoperative dosages of insulin varied between 0·5 and 1·0 units/kg at 09.00 hours and between 7·0 and 10·0 units per kg body-weight at 18.00 hours. *Fig. 2a* shows that, in unoperated animals, this procedure effectively produced normal blood glucose levels over the entire 24-h period. The insulin requirement was strongly reduced after operation. For instance, the total amount of insulin needed by rats in the insulin-1 group on the first postoperative day varied between 0 and 1 units/kg, resulting in a mean(s.d.) blood glucose level of 5·3(2·4) mmol/l ($n = 20$) at 09.00 hours on day 2. Although

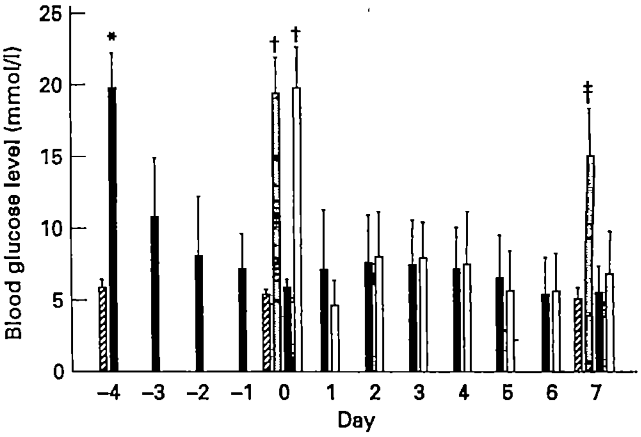

Fig. 1 Non-fasting blood glucose levels. Values are the mean(s.d.) of measurements performed in 09.00 hours in the 7-day groups. ▨, Control group ($n = 10$); □, diabetic group ($n = 9$); ■, insulin-1 group ($n = 10$); □, insulin-2 group ($n = 9$). $^*P < 0{\cdot}017$ *versus* control group; $^\dagger P < 0{\cdot}017$ *versus* control and insulin-1 groups; $^\ddagger P < 0{\cdot}017$ *versus* all other groups (Wilcoxon rank sum test)

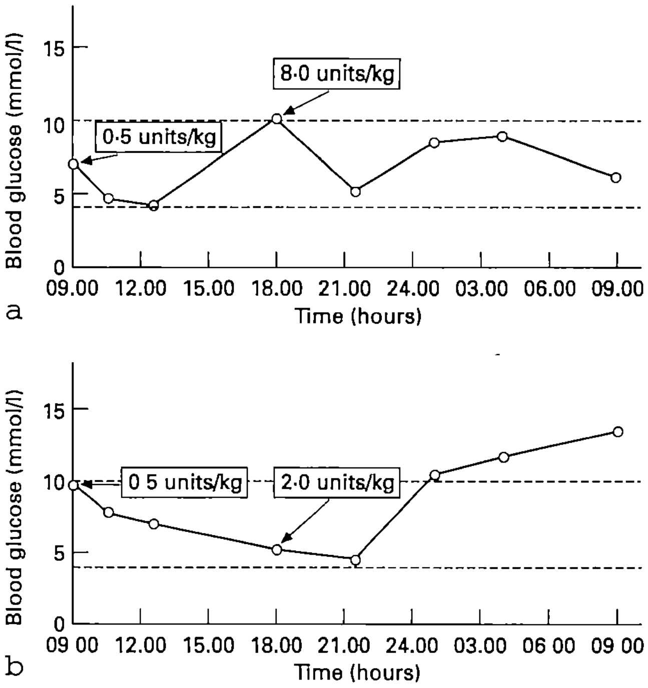

Fig. 2 Blood glucose control over a 24-h period, showing typical examples for blood glucose values in streptozotocin-treated rats a before and b 2 days after operation. The doses of insulin are also given. Dashed lines show the normal range for blood glucose concentration

strict control of blood glucose concentration within the normal range became more difficult (*Fig 2b*), mean non-fasting blood glucose values in both insulin-treated groups were within the normal range (*Fig. 1* for 7-day groups).

Body-weight

Changes in body-weight during the experiment are depicted in *Fig. 3*. After 3 days body-weight in the experimental groups was significantly ($P < 0.005$) lower than that in the control group. Preoperative administration of insulin restored weight gain. On the day of operation body-weight of animals in the diabetic and insulin-2 groups was significantly ($P < 0.0001$) lower than that of those in the control and insulin-1 groups.

Anastomotic abscess formation

The total number of anastomotic abscesses, observed in the ileum and colon within each group, is shown in *Table 1*. In the control group only one abscess was found. Uncontrolled diabetes significantly increased the frequency of abscess formation. The insulin-1 regimen almost completely prevented the development of this infectious complication, whereas postoperative administration showed only a limited beneficial effect.

Bursting pressure

The individual measurements of bursting pressure, in relation to bursting site and abscess formation, are shown in *Fig. 4*. Three anastomoses were damaged by the investigator during the assay procedure and were excluded from analysis. Several anastomoses in the diabetic and insulin-2 group had ruptured spontaneously during the course of the experiment. These bursting pressures were zero. Mean bursting pressures (*Table 2*) in the diabetic group were strongly ($P < 0.017$) reduced in both ileum and colon when compared with the control group. The insulin-1 regimen completely prevented this reduction of anastomotic strength. At day 3 the insulin-2 group showed

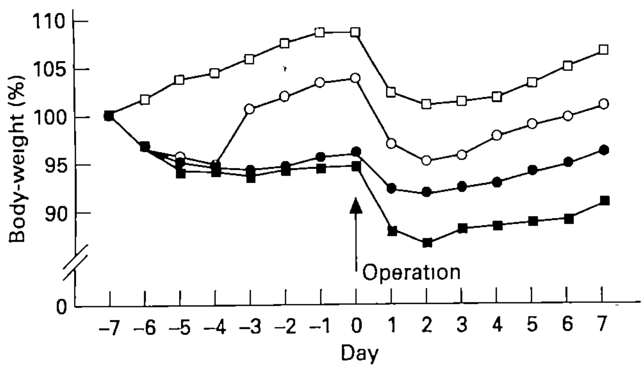

Fig. 3 Course of body-weight. Data represent mean values, calculated as the percentage of initial body-weight, in the 7-day groups □, Control group; ■, diabetic group, ○, insulin-1 group (insulin from day −4); ●, insulin-2 group (insulin from day 0)

Table 1 Anastomotic abscess formation

	Day 3		Day 7	
Group	Anastomoses	Abscess	Anastomoses	Abscess
Control	20	1	20	0
Diabetic	22	11*†	18	4
Insulin-1	20	2	20	0
Insulin-2	14	6‡	18	3

Values pertain to ileal and colonic anastomoses *$P = 0.0017$ (diabetic *versus* control group), †$P = 0.007$ (diabetic *versus* insulin-1 group); ‡$P = 0.012$ (insulin-2 *versus* control group) (two-tailed Fisher's exact test)

Table 2 Anastomotic bursting pressure

	Bursting pressure (kPa)			
Group	*n*	Ileum	*n*	Colon
Day 3				
Control	10	8.1(2.9)	10	18.1(5.8)
Diabetic	10	1.0(1.4)*	11	4.9(4.7)†‡
Insulin-1	10	9.9(4.5)	10	20.7(7.9)
Insulin-2	7	10.9(7.5)	7	10.2(6.4)‡
Day 7				
Control	9	44.9(8.7)	10	30.7(3.0)
Diabetic	9	13.6(16.3)†‡	8	20.5(8.6)†‡
Insulin-1	10	43.8(7.6)	10	34.2(4.2)
Insulin-2	9	30.1(13.3)†‡	9	24.7(3.4)†‡

Bursting pressure values are mean(s.d.). *$P < 0.017$ *versus* all other groups; †$P < 0.017$ *versus* control group; ‡$P < 0.017$ *versus* insulin-1 group (Wilcoxon rank sum test)

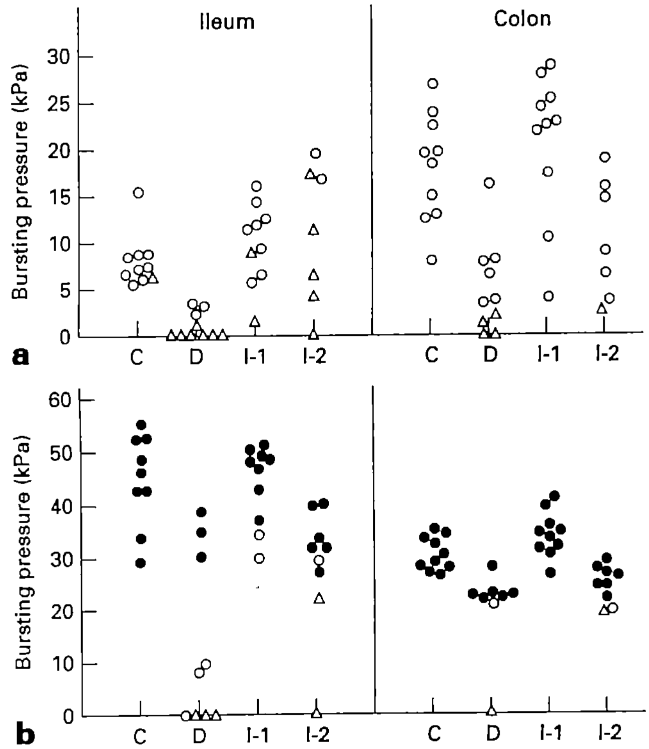

Fig. 4 Bursting pressure, bursting site and abscess formation at a 3 days and b 7 days after operation. Points represent the strength of individual anastomoses in control (C), diabetic (D), insulin-1 (I-1) and insulin-2 (I-2) groups. ○ and △, Rupture within the anastomosis; ●, rupture outside the anastomosis; ○ and ●, no abscess present; △, abscess present

normal anastomotic strength in the ileum. However, although the mean bursting pressure in colonic anastomoses was higher than in the diabetic group, it was still reduced by 44 per cent compared with that in the control group. All 3-day segments ruptured within the suture line. At 7 days, anastomoses in the control group had invariably grown stronger than the adjacent tissue: the bursting site was always outside the anastomotic area. This gain in strength was severely inhibited in animals with uncontrolled diabetes, particularly so in the ileum where six of nine anastomotic segments ruptured within the actual wound area. Again, the insulin-2 regimen seemed insufficient to restore healing completely as rupture occurred within the suture line in a total of five cases.

Discussion

Impaired wound healing is a postoperative complication commonly encountered in patients with diabetes mellitus. Clinical[1,14] and experimental[2,3,5,9] evidence for poor healing is derived mainly from skin wounds. Despite the absence of clinical evidence[15] diabetes is generally presumed to also impair intestinal healing and this assumption was recently confirmed by Gottrup and Andreassen[16], who studied repair of linear incisions in the stomach and duodenum of streptozotocin-induced diabetic rats; breaking strength in the duodenum was reduced by 26 and 33 per cent at 7 and 20 days after operation respectively[16].

The present data show that untreated streptozotocin-induced diabetes severely lowers anastomotic strength: 3 days after operation anastomotic bursting pressure was reduced by 88 per cent in the ileum and by 73 per cent in the colon. Moreover, complete anastomotic failure was evident in many untreated diabetic rats. It seems that the loss of strength of intestinal anastomosis constructed in a diabetic animal is far greater than that reported for linear incisions in the upper gastrointestinal tract[16] or skin[2-5]. Thus, the presence of uncontrolled diabetes must be considered a primary risk factor for anastomotic repair.

Although it is generally believed that good control of diabetes in the perioperative period promotes healing[17], this strategy is often not vigorously practised, possibly because the absence of clear evidence for such a strategy results in a lack of enthusiasm by clinicians.

Data on the efficacy of insulin treatment in restoring normal wound strength in experimental diabetes are equivocal. If insulin treatment is started immediately after induction of diabetes, the strength of incisional wounds in skin or duodenum equals that of controls[4,16], and Yue *et al.*[5] suggested, without showing actual data, that insulin improved wound strength in a dose-dependent manner. However, more recent data on skin wounds indicate that insulin cannot fully prevent the inhibitory effects of diabetes in either streptozotocin-induced or genetically diabetic rats, and it was concluded that diabetes causes structurally deficient wound healing even when the blood sugar level is returned to normal with insulin[9]. This conclusion is perhaps supported by the findings of Andreassen and Oxlund[4], who reported that insulin treatment from the fifth preoperative day was not sufficient to prevent the inhibitory effects of diabetes in the early phase of cutaneous wound repair.

The present results indicate that anastomotic healing in both the ileum and colon of diabetic animals proceeds undisturbed if hyperglycaemia is tightly controlled from 4 days before operation onwards. It must be emphasized that, in contrast to most experimental studies, particular care was taken to establish optimal control of blood sugar levels in each animal with a very long acting insulin, as required in the rat[18]. This is especially important on the first days after operation when the insulin need is low and may vary widely between animals. It remains to be established whether less careful diabetic control, for example by administration of a fixed dose of insulin over the entire experimental period (a procedure regularly adopted in other reported experiments[2,3,5]), will result in less complete restoration of anastomotic repair.

Insulin treatment from the day of operation onwards does not seem sufficient to result in normal anastomotic healing. Although ileal wound strength in the insulin-2 group equalled control values at day 3, this was not the case for the colon. Furthermore, the incidence of abscess formation remained high, particularly in the ileum. After 7 days the mean bursting pressures in the insulin-2 group remained significantly below those in the control and insulin-1 groups. At this time the bursting site is mostly outside the suture line, so these values represent the strength of the uninjured adjacent bowel wall rather than that of the anastomotic area. Apparently a period of uncontrolled hyperglycaemia reduces the strength of the intestinal wall. It could be that hyperglycaemia enhances non-enzymatic glycosylation of proteins including collagen[19,20], a process that is poorly reversible and results in disturbed intermolecular crosslinking[21] and subsequent loss of submucosal strength.

The reduced strength of wounds in diabetic animals is attributed to impaired accumulation of collagen[2,22,23]. Contrary to these findings, it was established that this was not the case for intestinal anastomoses: loss of strength was not accompanied by a lowered anastomotic collagen content[13,24]. Presumably, a qualitative change in newly formed collagen causes the reduction in wound strength.

The results from an earlier series of experiments[13] suggested that anastomotic abscesses were a consequence rather than the cause of diminished anastomotic strength in diabetic animals. This hypothesis appears to be strengthened by the present results. Although *Fig. 4* indicates that in individual anastomoses the presence of an abscess was often attended by a low bursting pressure, this was not invariably the case: 3 days after operation the mean anastomotic strength was normal in the ileum of the insulin-2 group, while five of seven anastomoses showed abscesses. Also, in the colon the insulin-2 regimen led to a reduction in the number of abscesses without fully restoring anastomotic strength.

Hypovolaemia as a cause for weight loss is unlikely to contribute significantly to poor healing: Foster *et al.*[25] reported that a 10 per cent loss of circulating volume did not reduce the strength of colocolic or ileocolic anastomoses in rats. Yue *et al.*[5] concluded that a comparable diabetes-induced loss of weight had no independent effect on cutaneous wound strength: malnutrition over 8 weeks was more important than actual weight loss. Moreover, malnutrition impairs wound healing but to a much lesser degree in colonic anastomoses than in skin wounds[26]. Because rats in the present experiment were fed *ad libitum* and the experimental period was only 2 weeks, neither malnutrition nor weight loss appears sufficient to explain the observed differences in wound strength. Also, local administration of insulin to skin wounds restores the normal healing response in rats with uncontrolled diabetes and concomitant weight loss[23]. Thus, although changes in body-weight apparently parallel the degree of intestinal healing, a causal relationship seems unlikely.

These studies show that uncontrolled diabetes severely reduces early anastomotic strength. Optimal control of blood sugar concentration by administration of insulin from 4 days before operation onwards may prevent this effect, but postoperative diabetic control alone is insufficient to restore adequate healing fully. It remains to be established to what extent less strict control of blood sugar levels in the perioperative period or preoperative insulin therapy alone may affect normal anastomotic repair.

Acknowledgements

The authors are grateful to Dr J. A. Lutterman, Department of Internal Medicine, University Hospital Nijmegen, for helpful discussion and providing insulin, and to the Department of Medical Statistics for statistical evaluation of the data.

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British Journal of Surgery 1996, 83, 1722–1724

Pitfalls in the management of preauricular sinuses

A. R. CURRIE, W. W. K. KING, A. C. VLANTIS and A. K. C. LI

Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong
Correspondence to: Professor A. K. C Li

A total of 159 operations for the excision of a preauricular sinus carried out in 117 patients over an 8-year period were reviewed. Previous excision, the use of a probe to delineate the sinus and operating under local anaesthesia all increased the chance of recurrence. The condition recurred more often in patients who developed postoperative wound sepsis than in those who healed primarily. Means of decreasing the recurrence rate include: (1) meticulous dissection of the sinus by an experienced head and neck surgeon under general anaesthesia; (2) the use of an extended preauricular incision; (3) clearance down to the temporalis fascia to ensure complete removal of all epithelial components; (4) avoidance of sinus rupture; and (5) closure of wound dead space.

While many preauricular sinuses remain asymptomatic, a minority discharge or become infected, causing pain and swelling (*Fig. 1*). Treatment of acute infection or abscess is adequate drainage, if indicated, and culture-directed antibiotics until all sepsis has cleared. When symptoms are recurrent, excision of the sinus with its tract is the treatment of choice. Best done once the inflammation has settled, the aim of surgery is to extirpate all squamous epithelium that forms the lining of the sinus. The sinus may have extensive and deep branching ramifications, so, unless completely removed, the residual squamous epithelium will form a recurrent sinus. After simple elliptical excision around the sinus opening and limited dissection of the tract, the reported recurrence rate varies from 26 per cent[1] to 42 per cent[2]. In Hong Kong, where the condition is common, 117 patients underwent 159 operations over 8 years at the Prince of Wales Hospital. This study assesses the factors that influenced the outcome following surgical excision.

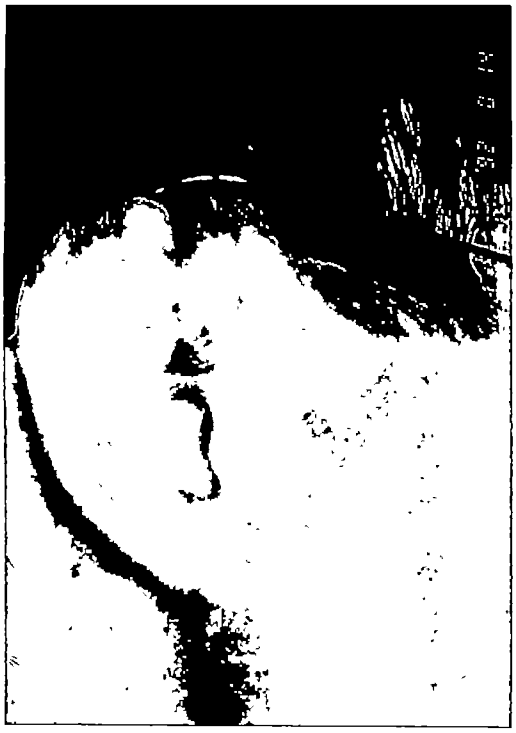

Fig. 1 Infected preauricular sinus with recent incision and drainage

Paper accepted 9 March 1996

Patients and methods

The hospital medical records of all patients who had excision of a preauricular sinus between 1984 and 1991 were analysed. Only classical preauricular sinuses were studied. Bilateral procedures were regarded as separate operations.

Patients were classified into those who healed primarily, those who developed postoperative wound infection but eventually settled, and those who had a recurrence. The definition of recurrence included further symptoms such as a subcutaneous mass, a persistently draining sinus or a resurgence of sepsis after initial healing had taken place.

Results

During the study 117 patients were scheduled for excision of a preauricular sinus. There was no seasonal variation in the operation rate. The male to female ratio was 2:3. Median age of the patients was 12 years (ranging from a few months to 80 years). Some 77 patients (66 per cent) were under the age of 15 years and 111 (95 per cent) were aged less than 40 years. Sinuses were generally as common on the right (35) as on the left (40) and were present bilaterally in approximately one-third of patients (42).

Indications for operation included previous sepsis (130) with or without a history of incision and drainage for a preauricular abscess (44) or previous attempted excision (20). Some 19 sinuses were recurrent. Two patients had had two previous excisions. Twenty-nine asymptomatic

Table 1 Previous sinus sepsis in 117 patients (159 operations)

Previous history	No. of sinuses
Sepsis only	79
Sepsis and incision and drainage	31
Sepsis, incision and drainage, and excision	13
Sepsis and excision	7
No sepsis	29

Table 2 Previous history and outcome

	Healed (%)	Sepsis rate (%)	Recurrence rate (%)	Unknown (%)	*n*
Previous excision	55	20	33	10	20
Previous sepsis	51	33	17	11	130
Previous incision and drainage	42	35	10	9	44
All sinuses	53	29	19	14	159

Table 3 Technique and outcome

	Healed (%)	Sepsis rate (%)	Recurrence rate (%)	Unknown (%)	*n*
Probe	56	30	36	7	27
Diathermy	53	35	18	6	17
Methylene blue	56	13	13	19	16
All sinuses	53	29	19	14	159

sinuses were also excised at the time of surgery for a symptomatic contralateral sinus (*Table 1*).

A total of 159 operations were performed on 117 patients. In 58 of the operations both sides (asymptomatic and symptomatic sinuses) were excised at the same time. General anaesthesia was used in 69 per cent of patients and local anaesthesia in the remainder. A probe was used to delineate the tract in 27 operations, methylene blue was used in 16 and diathermy was employed for tract dissection in 17.

Median follow-up was 11 weeks (range from a few weeks to 6 years). Follow-up details were not available for 32 operated sinuses. Primary healing of the wound was achieved in 83 sinuses. Postoperative wound sepsis occurred in 46; in nine of these incision and drainage was required. Recurrence occurred in 30 operated sinuses, 19 of which had postoperative wound sepsis. However, postoperative wound sepsis did not invariably result in recurrence: only 43 per cent of patients who had immediate postoperative wound sepsis developed further symptoms.

Recurrence was most common in patients in whom previous excision had been attempted (33 *versus* 19 per cent for all sinuses; *Table 2*), where a probe was used to define the tract (36 *versus* 19 per cent for all sinuses; *Table 3*) and where local anaesthetic was used (30 *versus* 12 per cent for general anaesthesia). Note that in *Tables 2* and *3* each operated case can belong to more than one category of outcome.

Discussion

The external ear develops from three hillocks of mesoderm covered by ectoderm that form on each of the caudal and rostral lips of the first branchial groove. A preauricular sinus is thought to result from entrapment of ectodermal epithelium in the first branchial arch elements of the external ear[1]. This congenital abnormality does not involve the depths of the first branchial groove, which contributes to the formation of the external auditory meatus and tympanic membrane. Preauricular sinuses therefore do not involve these latter structures or the facial nerve. They may lead to a subcutaneous cyst that is multi-branched and intimately related to the groove between the tragal cartilage and the anterior crus of the helix, to the extent that it is often difficult to separate the sinus from the cartilage or at least the perichondrium of the pinna. It lies at the level of, or above the arch of, the zygoma and its deep relation is the temporalis fascia.

Preauricular sinus may be associated with various other congenital deficiencies such as deafness. Renal anomalies have been reported to be significantly more common in patients with a preauricular sinus (4·3 per cent) than in the general population (1 per cent)[3].

Although the incidence of preauricular sinus has been reported to be 0·06 per cent in Scotland, 0·23 per cent in New York[1], 0·47 per cent in Hungary[4] and 2·5 per cent in Taiwan[5], the true incidence is not well documented. This is possibly because many are asymptomatic and patients present for treatment only when infection develops.

In this series the incidence of postoperative wound sepsis was 29 per cent and the recurrence rate 19 per cent. These values are similar to those in a previous report[6] but are reduced by the use of perioperative antibiotics, by suture closure of the sinus opening before excision and by precise dissection of the sinus to avoid an epithelial breach. For this purpose, operative magnification is an advantage. Recurrence, variously reported from nil[6,7] to 26 per cent[1] and 42 per cent[2], is the result of residual viable squamous epithelial remnants, as the sinus is usually multilocular. These epithelial islands derive from the tract from which operative spillage of sinus contents containing viable squamous cells and organisms takes place. The high recurrence rate may also be related to the fact that a preauricular sinus is often regarded as a minor condition and surgery is delegated to inexperienced surgeons.

A probe has been employed to trace the tract[2]. However, because the communications between the loculations are narrow, it is unsuitable for reliable delineation of the whole sinus. There was a high recurrence rate of 36 per cent in patients in whom a probe was used to delineate the tract. The use of cautery to destroy the epithelium rather than surgically excising it is of no value[1]. Methylene blue has been advocated to delineate the sinus and in this series a low recurrence rate of 13 per cent was observed in patients in whom it was used (*Fig. 2*). However, methylene blue does not stain the epithelium itself and, if spilled, contaminates the operative field. With an operating microscope, spillage of methylene blue is not a problem as the epithelium remnant can still easily be identified[7].

An important feature of preauricular sinuses is the close relationship between the sinus wall and the cartilage of the helix. It is advisable, using sharp dissection, to resect a portion of perichondrium or cartilage to ensure complete removal of the epithelial lining[2,6].

The sinus always lies lateral to the temporalis fascia. The surgeon should regard this as the medial margin and the cartilage as the posterior extent of the dissection. Remaining posterior to the superficial temporal artery should ensure the safety of branches of the facial nerve. An extended preauricular excision will aid exposure and allows the surgeon to get down easily to the plane of the superficial temporalis fascia cephalad to the area of scarring and fibrosis (*Fig. 2*). All cystic structures and fibrotic tissues can then be completely cleared away from the temporalis fascia. Once the sinus has been excised, the

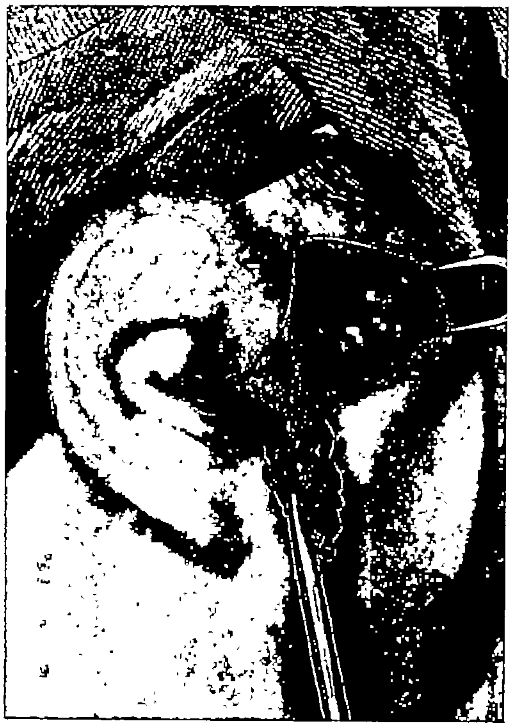

Fig. 2 Extensive preauricular sinus in the same patient excised via preauricular incision (tract was delineated by methylene blue). For complete excision, the dissection extends down to temporalis fascia

resulting dead space is difficult to close. Use can be made of a layered closure, drainage (either simple or suction) or a pressure dressing.

Treatment of an asymptomatic sinus is unnecessary; most remain asymptomatic. In this series, three of the 29 asymptomatic sinuses that were excised because surgery on the symptomatic contralateral side was being performed, developed postoperative sepsis.

General anaesthesia is obligatory, as patients are much more comfortable and the surgery can last over 2 h, especially when both sides require operation. General anaesthesia also facilitates the sterile draping of the face. In this series the low recurrence rate of 12 per cent was observed in patients undergoing excision under general anaesthesia.

Preauricular sinuses are a relatively common problem and, unless treated properly, may recur. Sepsis should be controlled by appropriate treatment before surgery, and the use of perioperative antibiotics is advisable. General anaesthesia is obligatory. Adequate identification of the sinuses is achieved with an extended preauricular incision and the aid of magnification. Attempts to outline the sinuses by probing are unhelpful. There should be precise dissection down to the superficial layer of the temporalis fascia, and the excision should include some perichondrium and possibly cartilage. It is important to close dead space as completely as possible by means of a layered closure with, or without, a drain or a compression bandage.

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British Journal of Surgery 1996, 83, 1725–1728

Colour-coded duplex imaging can safely replace diagnostic arteriography in patients with lower-limb arterial disease

M. PEMBERTON, S. NYDAHL, T. HARTSHORNE, A. R. NAYLOR,
P. R. F. BELL and N. J. M. LONDON

Department of Vascular Surgery, Clinical Sciences Building, Leicester Royal Infirmary, Leicester LE2 7LX, UK
Correspondence to. Mr N. J. M. London

The purpose of this study was to review the outcome of adopting colour-coded duplex ultrasonography as the primary imaging modality in patients with symptomatic lower-limb arterial disease. Over a 12-month period 467 consecutive lower-limb duplex scans were performed of which 437 (94 per cent) were technically adequate. Of the 467 limbs, 184 (39 per cent) were managed conservatively, 230 (49 per cent) were referred for percutaneous transluminal angioplasty (PTA), 41 (9 per cent) underwent reconstructive surgery and 12 (3 per cent) required diagnostic arteriography. In patients referred for PTA there were only 22 (10 per cent) unexpected findings; there was agreement about superficial femoral artery occlusion length in 95 (89 per cent) of 107 limbs and about the presence or absence of a superficial femoral artery stump in 91 (85 per cent) of 107 cases. In patients referred for surgery there were no unexpected findings. Colour-coded duplex imaging can safely replace diagnostic arteriography in up to 97 per cent of lower limbs with arterial disease.

Duplex ultrasonography possesses both theoretical and practical advantages over arteriography as an imaging modality for lower-limb arterial disease[1]. In particular, duplex imaging provides information on both the anatomical site and haemodynamic impact of individual atherosclerotic lesions, whereas arteriography gives only anatomical information. Furthermore, duplex ultrasonography is non-invasive, relatively cheap and is not associated with the serious complications that sometimes arise from arteriography[2,3]. Although a number of recent studies have shown that lower-limb arteries may be imaged successfully by colour-coded duplex scanning and that duplex findings correlate well with the results of arteriography[4–9], only one[10] has addressed the issue of patient management based primarily on duplex ultrasonography. The purpose of this study, therefore, was to review the outcome of adopting colour-coded duplex ultrasonography as the primary imaging modality in patients with symptomatic lower-limb arterial disease.

Patients and methods

The notes of all patients who had been referred for lower-limb colour-coded duplex scans between 1 October 1993 and 30 September 1994 were reviewed. During this interval, all patients with symptomatic lower-limb arterial disease that merited investigation were referred for duplex imaging. If the colour duplex assessment was technically unsatisfactory, patients had diagnostic arteriography. Although the clinician who requested the scan would usually require the entire limb to be assessed, on occasion a limited scan was ordered to confirm the suitability of a segment to provide either inflow (for femoral crossover grafts) or outflow, in evaluating treatment options. On the basis of colour duplex scans, patients were either managed conservatively or referred for percutaneous transluminal angioplasty (PTA) or surgery.

Duplex scans were performed by one of three vascular technologists working in the Vascular Studies Unit using an ATL Ultramark 9 duplex scanner with a colour-coding facility (Advanced Technology Laboratories, Bothell, Washington, USA). The results of duplex scans were recorded on a standard pro forma. When iliac scans were requested, patients were asked to attend starved for 6 h. Iliac segments were examined with a 3 5-MHz probe with the patient supine. A 5-MHz probe was used for the femoropopliteal arteries, which were scanned with the legs relaxed in slight external rotation. Insonation of the popliteal arteries and the origins of the tibial arteries was performed in a lateral position with the knees flexed. The infrapopliteal vessels were similarly scanned with a 5-MHz probe with the patient either supine or in a lateral position.

Arterial lesions were located by changes in colour flow patterns, changes in vessel diameter (on B mode) and broadening of the Doppler spectrum, whereas stenoses were quantified by measuring the peak systolic velocity (PSV) ratio across a lesion: by comparing the PSV within a stenosis to that in the nearest disease-free segment, a ratio was created that was independent of individual variations in blood pressure, vascular compliance and cardiac function. A PSV ratio greater than 2 was considered to define a significant stenosis[11,12]. Vessels were considered to be occluded if no colour flow could be detected and no pulsatile flow was present with the pulsed Doppler Approximately 20 per cent of scans were performed at the initial outpatient visit; the remainder required a separate appointment.

Diagnostic arteriography was performed by means of a Seldinger technique. The majority of pictures were uniplanar, but in some instances the aortoiliac arteries were imaged in two planes. Digital subtraction was used routinely. In the case of PTA, the radiologist examined the duplex map and planned the approach based on the distribution of disease. Diagnostic arteriography was not performed routinely before PTA.

A peroperative papaverine test was performed when duplex findings indicated iliac stenosis of borderline significance. Before femorodistal procedures, run-off was assessed by dependent Doppler imaging[13], which was used to determine which crural vessel provided the largest contribution to the pedal arch. Duplex ultrasonography was used to determine the best site for insertion of a graft on to this vessel All femoropopliteal or femorodistal procedures were assessed by on-table pre-reconstruction arteriography and completion arteriography. Patients who had surgery within 3 months of arteriography during failed PTA were not included, even when duplex imaging was done.

Presented to the Vascular Surgical Society of Great Britain and Ireland, London, November 1995
Paper accepted 13 July 1996

Results

During the 1-year study 329 patients were referred for a duplex scan. The median patient age was 69 (range 30–94) years, 221 (67 per cent) were men and 37 (11 per cent) patients were diabetic. Some 138 patients had bilateral scans; therefore 467 limbs were examined. The clinical indication was claudication in 355 (76 per cent), ischaemic rest pain in 69 (15 per cent) and tissue loss in 43 (9 per cent) of the limbs scanned.

Complete aorta to ankle scans were performed in 345 cases (74 per cent) and, on the basis of a normal femoral artery waveform, 54 limbs (12 per cent) were scanned from the inguinal ligament to the ankle. At the request of the referring clinician, 15 examinations (3 per cent) were limited to the iliac artery and 16 (3 per cent) to the infrapopliteal arteries. In 37 limbs (8 per cent), all of which needed scans for claudication, below-knee examinations were incomplete for logistical reasons (22 cases) or were not performed at all (15).

Duplex examination was technically successful in 437 limbs (94 per cent). Although some were reported as 'difficult', only three (1 per cent) of 396 iliac scans were unsuccessful. Femoropopliteal segments (435) were characterized completely in all cases, whereas infrapopliteal segments could not be imaged completely because of ulceration or calcification in 26 (6 per cent) of 414 limbs.

Clinical outcome

Twelve limbs (3 per cent) required diagnostic arteriography, 184 (39 per cent) were managed conservatively, 230 (49 per cent) were referred for PTA and 41 (9 per cent) for surgery (*Table 1*). The median interval between duplex imaging and surgery was less than 1 week. There were no unexpected findings at operation. The three on-table papaverine tests that were performed confirmed significant iliac stenosis, as indicated by duplex ultrasonography. On-table pre-reconstruction arteriography confirmed the suitability of the run-off vessel selected to receive a graft on the basis of duplex imaging in all cases. There were no postoperative complications resulting from inadequate duplex information provided at the time of operation. Most infrainguinal grafts were systematically followed in a graft surveillance programme (21 of 26 grafts); the patency rate was 86 per cent at 3 months with failures attributed to poor vein quality.

A further 70 limbs that were revascularized over the study interval were not included. Of these, diagnostic arteriography had been performed either because the patient was on the surgical waiting list before the adoption of the duplex policy (20 limbs) or because arteriography had been performed in other centres (five limbs). Some 44 limbs came to surgery within 3 months of angiography (usually limited) performed during PTA; one limb was urgently revascularized without any preoperative imaging.

Table 1 Type of lower-limb vascular surgery performed in 41 limbs on the basis of duplex imaging alone

Operation	No performed
Aortobifemoral bypass graft	2
Axillobifemoral bypass graft	1
Iliofemoral bypass	3
Iliofemoral crossover bypass	4
Iliopopliteal bypass	1
Femoral above-knee popliteal bypass	8
Femoral below-knee popliteal bypass	8
Femorodistal bypass	6
Amputation	2
Combination of the above or other procedure	3

There were 22 (10 per cent) unexpected findings in the 230 limbs referred for PTA. The most common ($n = 12$) was stenosis found at angioplasty that had not been identified by duplex ultrasonography (one iliac, one superficial femoral artery (SFA), one profunda, nine infrapopliteal). On ten occasions a stenosis identified by duplex imaging had progressed to an occlusion (three iliac, two common femoral and five SFA). For SFA occlusions (107 cases), an estimate of the agreement on occlusion length was made between duplex ultrasonography and arteriography. In 12 cases (11 per cent) this difference was more than 2 cm, with duplex imaging measuring the occlusion shorter than arteriography in 11 and longer in one case. There was agreement between the two modalities with regard to the presence or absence of an SFA stump in 91 cases (85 per cent). In no case was a stump seen at arteriography but not by duplex imaging. Lesions characterized by duplex ultrasonography that were thought to be suitable for PTA had a successful angioplasty in 206 cases (90 per cent), with a median interval between duplex scanning and PTA of 22 weeks. No serious adverse clinical outcome was identified as a consequence of this policy.

Discussion

The majority of publications concerning lower-limb duplex imaging have compared duplex ultrasonography with arteriography[4–9,11]. Although this has shown that duplex imaging correlates well with arteriography, it is constrained by the definition of arteriography as the 'gold standard' – so colour duplex imaging could be only second best. It was decided, therefore, to evaluate the potential of duplex ultrasonography by using it as the principal imaging modality for peripheral arterial disease and to review the clinical outcome. Although a similar approach has recently been reported by Elsman *et al.*[10], diagnostic arteriography was used to 'confirm the duplex results' in the majority of patients, whereas the present authors elected to use diagnostic arteriography only when duplex imaging was unsuccessful.

The technical success rate of duplex imaging in the present study was 94 per cent and, although concern about the use of duplex scanning in the aortoiliac segments has been expressed[14], it was found that only three (1 per cent) of 396 aortoiliac segments could not be visualized. While the presence of overlying bowel gas can make identification of iliac pathology difficult, the view can often be improved by repositioning the patient or returning to the site of difficulty later in the examination, thus allowing bowel gas to shift. To expedite the examination in some cases (54 limbs), a formal duplex scan of the aortoiliac segment was not performed but instead the common femoral artery waveform was analysed. Although this approach has been reported to be as accurate as aortoiliac arteriography[15–17], it remains a contentious issue[18,19] and requires further clarification. Problems posed by calcified vessels can make complete assessment of infrapopliteal arteries difficult, but calcification is usually non-concentric and can be overcome by insonating the vessel from a different angle. In case of concentric calcification, extensive ulceration and gross oedema, it may be impossible to visualize the infrapopliteal vessels, and the technical failure rate in this area was higher: 26 (6 per cent) of 414 limbs.

On the basis of the duplex findings alone, 184 limbs were managed conservatively: all were patients with claudication in whom lesions suitable for PTA had not been identified. It is accepted that among these patients correctable lesions may have been missed, although the low rate of missed suprageniculate lesions in patients actually referred for PTA suggests that the number would have been small. There were no unexpected findings in the 41 limbs referred for surgery and, more importantly, no postoperative graft occlusions attributable to failure of preoperative duplex imaging. However, limbs undergoing below-knee revascularization also had run-off assessed by dependent Doppler imaging[113]. Thus dependent Doppler ultrasonography was used to determine which vessel contributed most to the pedal arch, whereas duplex imaging was used to determine the optimal level for graft insertion. These findings were then confirmed by on-table pre-reconstruction arteriography.

There were 230 limbs referred for PTA and in 22 (10 per cent) there were unexpected findings. Many of these were infrapopliteal stenoses ($n = 9$) and did not cause any problems for the radiologist with respect to the site and direction of arterial puncture. On ten occasions the stenosis had progressed to occlusion, which probably reflects the delay between diagnostic duplex imaging and therapeutic PTA (median 32 weeks).

Agreement between SFA occlusion length and the presence or absence of an SFA stump was evaluated because these parameters are considered to be important predictors of PTA success[20–22]. With respect to occlusion length there was agreement between duplex scanning and arteriography at the time of PTA in 89 per cent of cases. In 11 of the 12 cases where there was disagreement, duplex imaging appeared to underestimate occlusion length. This may be a failing of arteriography rather than of duplex imaging because arteriography overestimates occlusion length as a result of underfilling by distal collaterals[5,20]. There was disagreement concerning the presence of an SFA stump in 15 per cent of cases. In all these cases the stump identified at duplex examination was 1 cm or less in length and was characterized as a 'short narrow channel'. This disagreement reflects either progression of the occlusive process or the greater sensitivity of duplex ultrasonography compared with arteriography for the detection of low flow. The high sensitivity (100 per cent) of duplex for the detection of an SFA stump means that all patients suitable for PTA based on this criterion would be identified.

The duplex scan was used by the radiologist to plan access for PTA and on many occasions, therefore, arteries reported as normal by duplex imaging will not have been imaged at the time of PTA. In the case of a duplex scan showing a normal aortoiliac segment and infrainguinal disease, an antegrade femoral puncture was used. The purpose of this study was not to compare duplex ultrasonography with arteriography, which has been done previously[11], but to adopt duplex imaging as the primary investigation and then to scrutinize the clinical outcome. No seriously adverse clinical outcomes have been identified as a consequence of this policy. The long-term clinical outcome in patients undergoing PTA was not studied because it would be impossible to ascertain whether late failure resulted from progression of a lesion missed at the original duplex examination or from the development of a new lesion.

The present results show that the use of colour-coded duplex imaging as the primary investigation in patients with symptomatic lower-limb arterial disease allowed safe management decisions to be made without recourse to arteriography in 97 per cent of cases: although 6 per cent of scans were technically incomplete, most were in patients with claudication and it was still possible to make a management plan based on technically adequate supragenicular scans. If these findings are confirmed, diagnostic arteriography could be displaced by duplex imaging, an investigation that may not only be more informative, but is more patient friendly and cost effective[23].

Acknowledgements

The authors thank Yvonne Sensier, Abigail Thrush, Haley Handford and Anne Reid from the Vascular Studies Unit for their contribution to the work in this paper.

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British Journal of Surgery 1996, 83, 1729–1734

Diagnosis and therapy of aortic prosthetic fistulas: trends over a 30-year experience

J. M. VAN BAALEN, A. B. KLUIT, J. MAAS, J. L. TERPSTRA and J. H. VAN BOCKEL

Department of Surgery, Section of Vascular Surgery, Leiden University Hospital, Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands
Correspondence to: Dr J. M van Baalen

A retrospective study was carried out of patients from a single institution over a 30-year period. Thirty-one patients presented with 33 fistulas, four non-enteric and 27 enteric. In 25 of 27 patients with a prosthesis-related enteric fistula gastrointestinal bleeding was present. Angiography revealed the fistula in five patients, endoscopy in three, and barium studies, echography and computed tomography each revealed one fistula. Six patients died before and five died during operation. In 20 patients various techniques were used for treatment. In-hospital mortality decreased from six of eight patients before 1970, to seven of ten between 1971 and 1980, and to four of 13 after 1981. In the long term, patients treated with an extra-anatomic reconstruction had a poorer prognosis than those treated by *in situ* reconstruction. This experience shows that diagnostic tests often fail to reveal a prosthesis-related fistula and that mortality can be substantially reduced by early exploration in patients with negative diagnostic studies.

A prosthetic fistula after aortic surgery is a rare but potentially fatal complication. The incidence of this complication ranges from 0·5 to 4 per cent[1–5]. It can be expected, in view of the present increase in aortic surgery, that this complication will be seen with increasing frequency. If a patient presents with gastrointestinal bleeding, it may be difficult to achieve timely and accurate positive diagnosis or exclusion of the presence of a fistula. From the literature no single test has emerged as effective in establishing the diagnosis of this complication. Furthermore, even if an aortic prosthesis-related fistula is diagnosed and treated appropriately, the results of surgery are often poor. This is partly due to the magnitude of the operation in frail patients and partly because of complications related to underlying prosthetic infection[6,7]. In 1953 Brock[8] described the first case of an aortoenteric fistula after reconstructive aortic surgery. Heberer[9] in 1957 performed the first successful repair of such a fistula. More recently, prosthetic removal and extra-anatomic bypass has been advocated as the standard treatment of prosthetic fistula[3,10,11]. Because of the high mortality rate associated with this procedure some have advocated *in situ* reconstruction as an alternative, which may provide a durable solution in selected cases[5,12–14]. This retrospective study presents the authors' experience with diagnosis and therapy in a large number of patients from a single institution over a period of 30 years.

Patients and methods

All patients submitted to arterial reconstructions in this department during the three decades to 1995 were followed by a surveillance programme with ultrasonography and, if appropriate, computed tomography (CT). All vascular reconstructions were retrieved and reviewed retrospectively. From these data all patients with an aortic prosthetic fistula were selected for this study. Data for 31 consecutive patients were obtained from clinical and outpatient records. All patients were treated by one of the senior vascular surgeons (J.M.v.B., J H.v.B. and J.L.T)

Results

Patients

Between 1965 and 1995, 30 men and one woman presented with a fistula after prosthetic reconstruction of the aortoiliofemoral tract. Two patients presented with a recurrent fistula, resulting in a total of 33 fistulas for evaluation. The age of the patients at the time of primary operation ranged from 15 to 77 years. The mean interval between primary operation and the diagnosis of fistula was 65 (range 2–297, median 150, interquartile range 74, first quartile 10, second quartile 60, third quartile 84) months. The primary operation was abdominal aortic aneurysm repair in 18 patients; eight aneurysms were ruptured. In 12 patients the primary reconstruction was performed for occlusive aortoiliac disease; in one it was for false aneurysm after kidney transplantation.

An aortobi-iliac prosthesis was inserted at the primary operation in 21 of the 31 patients; the other reconstructions included three aortobifemoral, three aortoiliofemoral, two iliofemoral, one aortofemoral and one aortic tube grafts. Before 1966 silk sutures were used in ten patients, from 1967 through 1976 braided Dacron (Du Pont, Stevenage, UK) was used in eight, and since 1976 monofilament polypropylene has been used in 13. The mean interval between primary operation and prosthetic fistula formation was 84 months for reconstructions with silk sutures, 73 months for those with braided Dacron, and 62 months for those with polypropylene. Patients were routinely seen for follow-up at 3, 6 and 12 months, and yearly thereafter. Physical examination was always performed and, from 1978, ultrasonographic studies were performed every 2 years to assess the anastomoses for false aneurysm formation.

Fistulas: location and symptoms

The anastomoses involved in fistula formation in 33 cases were the aortic (23), iliac (nine) and femoral (one). There were 29 aortoenteric fistulas, three ilioureteral fistulas and one aortocaval fistula. The enteric fistulas involved the duodenum in 19 cases, the jejunum or ileum in eight, the caecum in one and the sigmoid colon in one. The

Paper accepted 1 February 1996

relationship between the site of anastomosis and the organ involved is shown in *Table 1*.

Twenty-five of the 29 aortoenteric fistulas presented with gastrointestinal blood loss. This was microscopically evident in nine fistulas; eight were associated with melaena and eight with haematemesis. In 12 cases the first presentation was acute severe gastrointestinal haemorrhage, demanding emergency operation in ten. In 13 instances chronic blood loss resulted in anaemia or melaena. Symptoms lasted from several weeks to up to 10 months. In only 16 of the 31 patients were signs of infection, such as fever, leucocytosis, raised erythrocyte sedimentation rate, anaemia, infected groin wounds or positive blood cultures, present. In two patients (one ilioureteral, one aortocaval fistula) the fistula was an incidental finding. Signs and symptoms are summarized in *Table 2*.

Diagnostic procedures

In 12 patients no diagnostic procedures were performed; in ten massive gastrointestinal bleeding occurred, requiring emergency operation, and in two no graft-related fistula was suspected before operation. In the remaining 19 patients (21 fistulas) 36 diagnostic procedures were performed, of which only 11 were indicative of fistula. In one patient two examinations revealed a fistula, so in ten patients of 19 submitted to diagnostic procedures a fistula was discovered. Endoscopy was performed in 12 patients and only three aortoduodenal fistulas could be diagnosed. Angiography was performed in ten patients and revealed five prosthesis-related fistulas by leakage of contrast. In two of these cases an ilioureteral fistula and an aortocaval fistula were an incidental finding at angiography. CT using intravenous contrast agent and echography were performed in five cases and revealed only one fistula each. Barium studies were performed in four cases and revealed only one prosthesis-related fistula. The results of the diagnostic procedures are summarized in *Table 3*.

Table 1 Relationship between location of the fistula and site of anastomosis

	Site of anastomosis			
Site of fistula	Aortic	Iliac	Femoral	Total
Duodenum	18	1	0	19
Jejunum or ileum	4	4	0	8
Caecum	0	0	1	1
Sigmoid	0	1	0	1
Ureter	0	3	0	3
Inferior vena cava	1	0	0	1
Total	23	9	1	33

Table 2 Presenting symptoms and signs in patients with prosthesis-related fistula

Signs and symptoms	No of patients
Asymptomatic	2
Pain	
Without chronic infection*	1
With chronic infection*	6
Anaemia	13
Chronic infection*	16
Gastrointestinal haemorrhage	
Melaena	8
Haematemesis	8
Haematochezia	9

*Raised erythrocyte sedimentation rate, leucocytosis, fever and anaemia

Predisposing factors

In 20 of the 31 patients a possible predisposing factor for the development of fistula was present. One patient was operated on for ruptured mycotic (*Salmonella*) aneurysm; after 2 years, a prosthesis-related fistula developed and culture demonstrated *Salmonella* of the same type. Another predisposing factor was infected aortic aneurysm (*Staphylococcus aureus*) untreated with antibiotics during and after operation; 26 months later an aortoduodenal fistula developed and culture demonstrated the same micro-organism. A further factor was mycotic aneurysm (*Escherichia coli*) complicated by perforation of the sigmoid; 2 months later an aortoduodenal fistula developed with *E. coli* on culture. One patient, 5 days following aortic reconstruction for ruptured aneurysm, had a sigmoid colon perforation and infected haematoma which was treated with drainage, colostomy and antibiotics; 8 months later an ilioduodenal fistula developed. Another patient, originally treated for a ruptured aneurysm, was operated on because of melaena, and a colotomy was made in search of a sigmoid polyp. This was combined with exploration of the aortic anastomosis of a bifurcation graft; 1 month later he presented an aortoduodenal fistula. There was an instance of mycotic aneurysm (*Klebsiella*) in a patient who later (at 11 months) developed an intra-abdominal abscess caused by a perforated appendicitis; this was treated by drainage of the abscess, appendicectomy and antibiotics. Some 5 months later an aortoduodenal fistula presented with *St. aureus* on culture. One patient with peritonitis and pain in the right iliac fossa, suggesting appendicitis, was treated conservatively 3 months before presenting with a femorocaecal fistula. In another case chronic cholecystitis was noticed at the primary operation and cholecystectomy was performed before the retroperitoneum was closed; after 1 month an ilioileal fistula was noted. A further cholecystectomy was performed for acute cholecystitis 66 months before a fistula developed between an iliac anastomosis and the sigmoid. There was an instance in which the postoperative course of the primary operation was complicated by pneumonia; 80 months later an ilioureteral fistula was discovered. One patient had three aortic bifurcation grafts inserted because of recurrent thrombosis before an aortoduodenal fistula developed. Two patients had an infected aortic bifurcation graft treated by replacement before a fistula developed and in a further two a fistula recurred after treatment of a graft-related fistula. Finally, five remaining patients were treated primarily for ruptured aneurysm. The possible causes for prosthesis-related fistula are summarized in *Table 4*.

Treatment

Six patients died before operation could be performed and five died as a result of hypotension secondary to massive gastrointestinal bleeding at the time of emergency

Table 3 Diagnostic procedures in 33 prosthesis-related fistulas

Patient no.	Fistula no.	Year of operation	Endoscopy	Angiography	Ultrasonography	Computed tomography	Barium study
1*	1	1965	0	0	0	0	0
2	2	1968	0	0	0	0	+
3†	3	1969	0	0	0	0	0
4†	4	1969	0	0	0	0	0
5	5	1969	0	0	0	0	0
6†	6	1969	0	0	0	0	0
7*	7	1970	0	0	0	0	0
8†	8	1970	0	0	0	0	0
9*	9	1971	0	0	0	0	−
10	10	1972	0	0	0	0	0
11	11	1972	0	+	0	0	0
12	12	1972	−	−	0	0	0
13	13	1973	0	0	0	0	0
14†	14	1974	0	+	0	0	0
15*	15	1976	0	0	0	0	0
16	16	1976	0	+	0	0	0
17	17	1979	−	+	−	0	0
18†	18	1979	−	0	0	0	0
19	19	1981	−	0	0	0	0
20	20	1982	0	+	0	0	0
21*	21	1982	0	0	0	0	0
22	22	1982	−	0	+	0	0
23	23	1984	−	0	0	0	0
24	24	1984	−	0	0	0	0
25	25	1985	0	−	0	0	0
26	26	1989	+	0	0	0	−
26	27	1989	0	0	0	0	0
27	28	1990	0	−	−	−	−
28	29	1993	−	0	−	0	0
29	30	1994	−	−	−	−	0
30	31	1994	0	0	0	−	0
31	32	1994	+	0	0	+	0
27	33	1994	+	−	0	−	0

0, Study not performed; −, study performed, no fistula detected; +, study performed, fistula detected. *Died during operation; †died before operation

Table 4 Possible predisposing factors for the development of prosthesis-related fistula

Possible cause	No. of patients
Mycotic aneurysm	2
Mycotic aneurysm, sigmoid perforation	1
Sigmoid perforation, haematoma	1
Sigmoid resection, exploration aortic anastomosis	1
Cholecystitis	2
Appendicitis	2
Pneumonia	1
Third aortic prosthesis	1
Infected aortic prosthesis	2
Recurrent prosthetic fistula	2
Ruptured aneurysm without other pathology	5
Total	20

Table 5 Treatment of 31 patients with prosthesis-related fistula

	No. of fistulas	No. of patients
Died before reconstruction	11	11
Non-enteric fistula		
Extra-anatomic reconstruction	1	1
Anatomic reconstruction	3	3
Enteric fistula		
Extra-anatomic reconstruction		
Primary	6	6
Delayed	1	1
None	1	1
Anatomic reconstruction	8	8
Recurrent fistula, extra-anatomic reconstruction	1	
Recurrent fistula, anatomic reconstruction	1	
Total	33	31

surgery. Twenty patients survived the first operation for a prosthesis-related fistula. Of these 20, four presented with a non-enteric fistula. In two an ilioureteral fistula and in one an aortocaval fistula were treated by anatomic reconstruction. In one patient an ilioureteral fistula was treated by an extra-anatomic reconstruction, resection of the aortic graft and nephrectomy. Of the 16 patients with a prosthesis-related enteric fistula, partial or total resection of the prosthesis was performed in eight cases and the continuity of the vascular tree was re-established by a new prosthesis. In two patients the prosthesis-related fistula recurred. One of these patients subsequently underwent an extra-anatomic reconstruction and in the other the aortic prosthesis was replaced. In six patients excision of the prosthesis was followed by an extra-anatomic reconstruction; in two excision of the graft was not followed by extra-anatomic bypass. One of these latter

Table 6 Postoperative complications after the first operation for prosthesis-related fistula

Complication	No. of patients
Multiple organ failure	3
Cardiac failure	1
Disruption of aortic stump	2
Prosthetic thrombosis	3
Limb ischaemia	3
Abdominal abscess	2
Intra-abdominal haemorrhage	1
Incisional hernia	1
Compartment syndrome	1
Revision of colostomy	1

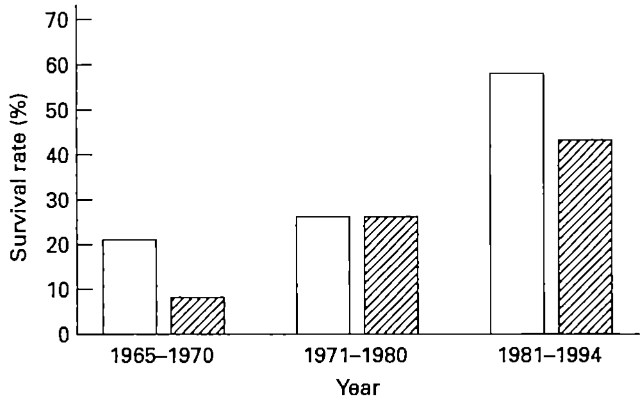

Fig. 1 Survival after reconstruction for a prosthesis-related fistula. □, Short-term survivor (discharged from hospital); ▨, long-term survivor (lived for 1 year or more after reconstruction)

patients underwent axillobifemoral bypass at a later date. The method of treatment of the 31 patients is summarized in *Table 5*.

Outcome

Reconstruction for a prosthesis-related fistula was performed in 20 of the 31 patients. Anatomic reconstruction was successfully performed in three patients with a non-enteric fistula. In one patient with a non-enteric fistula an extra-anatomic reconstruction was performed. This patient died from multiple organ failure. In eight patients with an enteric fistula an anatomic reconstruction was performed. One patient died in the postoperative period from myocardial infarction and two from multiple organ failure. During follow-up, three patients died from non-related causes at 10, 14 and 237 months. In eight patients with an enteric fistula an extra-anatomic reconstruction was performed. One patient died from multiple organ failure and two died after rupture of the oversewn aortic stump. After discharge from hospital a further three patients died from rupture of the aortic stump at 2 weeks, 3 and 6 months after discharge.

Thirteen patients were discharged from hospital after reconstruction for a prosthesis-related fistula with a mean hospital stay of 30 (range 12–84) days. In six the postoperative course was uncomplicated. In the remainder one or more reinterventions were necessary because of complications (*Table 6*). In two the prosthetic enteric fistula recurred; in one of these a new anatomic reconstruction was performed and in the other an extra-anatomic reconstruction was necessary. The latter patient died from multiple organ failure. The percentages of procedural and long-term (1 year or more after reconstruction) survivors for the various time periods are shown in *Fig. 1*.

Discussion

Aortic graft fistula is a rare but life-threatening complication after aortic reconstruction; the present series is one of the largest reported. The findings suggest that this complication may be related to the indication for and the course of the primary operation. Busuttil and co-workers[15] found an incidence of 0·17 per cent after elective resection of an aortic aneurysm and of 0·2 per cent after elective aortic reconstruction for occlusive disease, but 1·7 per cent after treatment of a ruptured aortic aneurysm. Bergqvist *et al.*[16] reported an incidence of 0·4 per cent after emergency reconstruction for aneurysmal disease, 0·5 per cent after operation for occlusive disease and 0·66 per cent after emergency reconstruction for ruptured aneurysm. In the present series, elective aneurysm repair constituted ten and elective operations for occlusive disease 12 of the 31 primary operations, whereas repair of ruptured aortic aneurysm constituted eight of the primary operations; one primary reconstruction was performed for false aneurysm. The primary procedures associated with prosthetic fistula reflect the authors' practice in the period studied. Over the study period approximately 1050 prosthetic reconstructions were performed for occlusive arterial disease and 1500 for aneurysmal disease. In this period the percentages of aortoiliac, aortofemoral and aortic tube grafts were respectively 80, 10 and 10 per cent. As some of the patients described in this series were referred from other hospitals, the incidence of prosthesis-related fistula is somewhat lower than that calculated from these values: approximately 1·2 per cent for aneurysmal disease and 0·7 per cent for obstructive disease.

In less than 2 per cent of patients presenting with gastrointestinal bleeding and in less than 1 per cent of those with an aortic prosthesis is haemorrhage actually related to a fistula[17]. In the present series gastrointestinal haemorrhage proved to be the most constant finding in patients with a prosthesis-related fistula. Bleeding was present in 25 of the 27 patients with a fistula between the aortic prosthesis and the intestine, and in 25 of all 31 patients with any prosthetic fistula. Symptoms of chronic infection were present in only 16 patients and only seven with a prosthetic fistula had abdominal pain. Therefore, gastrointestinal haemorrhage in a patient with an aortic prosthesis should give rise to a high index of suspicion of a prosthesis-related enteric fistula, even in the absence of signs and symptoms of chronic infection. Gastrointestinal bleeding after aortic reconstruction should be considered a prosthetic enteric fistula until proven otherwise.

A variety of diagnostic studies was used to demonstrate the presence of a fistula, but not all studies were performed in all patients and so sensitivity and specificity are difficult to determine. The selection of diagnostic studies was based on clinical appropriateness and availability; it reflects common clinical practice. Endoscopy is mandatory, either to evaluate more common causes of gastrointestinal haemorrhage or to diagnose a fistula[5,6,18,19]. However, as the fistula may arise from any segment of the intestine, both proximal and distal endoscopy should be considered. Endoscopic demonstration of gastrointestinal pathology other than a fistula or absence of endoscopic abnormalities does not exclude the presence of an aortoenteric fistula[10,18]. This is clearly illustrated by the fact that endoscopy performed in 12 of the present patients failed to reveal a fistula in nine. Even when endoscopy was performed during laparotomy and the suspicion of a fistula was high, the diagnosis was missed in two cases and only uncovered when the anastomosis was dissected.

Angiography is not usually considered useful in diagnosing a prosthesis-related fistula[19,20], but it is helpful in planning reconstruction. It has been suggested that a bulging dilatation at the aortic anastomosis is an indication of an aortic prosthesis-related enteric fistula in a small series of patients[21]. In the present series angiography demonstrated leakage of contrast agent in five of ten patients and detected most fistulas. However, in two patients the leakage of contrast agent was an incidental finding during routine angiography. CT with oral and intravenous contrast media may be more sensitive in detecting secondary changes at the anastomosis, compatible with a prosthesis-related fistula[22,23]. In the present series CT with intravenous contrast agent was performed in five patients with fistula and revealed only one such lesion. Magnetic resonance imaging (MRI) may become the tool of choice for diagnosing a prosthesis-related fistula[24–26].

The authors have engaged in a more aggressive diagnostic investigation in recent years in those suspected of having a prosthesis-related fistula but, even so, not all fistulas are diagnosed (*Table 3*). No single diagnostic technique can be recommended for all patients suspected of having a fistula. A combination of endoscopy and an imaging technique, such as CT, angiography or MRI, may offer the best chance of detecting a fistula, although this notion cannot scientifically be based on the results of the present series. Even if diagnostic investigation in a patient with gastrointestinal haemorrhage and previous abdominal aortic surgery does not show a fistula, laparotomy to exclude such a lesion should be considered[3,17,20]. In this series laparotomy was performed in ten patients for whom diagnostic studies failed to reveal a prosthesis-related fistula but in whom such a fistula was found at operation.

The present findings suggest that many fistulas may be preventable. Direct contact between bowel and prosthesis, erosion of the bowel by the prosthesis and destruction of the prosthesis are mentioned as important mechanical causes[15,27]. During operation the prosthesis should be tailored to prevent elongation and erosion of adjacent structures. Coverage of the entire prosthesis with retroperitoneal tissue or an omental flap to prevent direct contact between prosthesis and bowel, ureter or inferior vena cava may prevent the development of a fistula. The development of a fistula secondary to prosthetic infection has been described, especially in animal models[3,4,15,28]. A rigid antibiotic regimen in all patients submitted to vascular surgery and prevention of contamination of the prosthesis diminish the chance of the development of prosthetic infection. In the past the authors have routinely cultured the aneurysmal thrombus and wall. However, the number of positive cultures obtained was relatively low, which accords with the findings of other series, and the indication to treat patients with antibiotics if a positive culture is obtained remains debatable. The authors have refrained from this policy since 1989. The performance of intestinal procedures during the same operation as the implantation of a prosthesis should be performed only with great care and, even then, only after meticulous closure of the retroperitoneum.

Pseudoaneurysm formation has been suggested as a cause of aortic fistula[15,29–31]. False aneurysm may be detected by ultrasonography[32], which should be performed routinely during follow-up after aortic surgery. Various reports have dealt with the factors predisposing to the occurrence of prosthesis-related fistula; increased risk is recognized after complicated operations, repeat surgery or emergency aortic procedures[5,6,27,29].

The outcome of an untreated prosthetic enteric fistula is invariably death[4,19]; even with aggressive treatment the results are poor. Survival may be related to the timing of the operation and the technique employed to treat the fistula[20]. In the case of an infected prosthesis, local reconstruction[33], extra-anatomic reconstruction preceding or following excision of the aortic prosthesis[3,10,11], and excision of the aortic prosthesis and *in situ* placement of a new prosthesis[5,12–14] or alloprosthesis[34] have all been advocated. In the present series different techniques were used and all proved to be effective in solving the acute problem. Treatment was based on the extent of local infection found during operation. It is important to recognize that even in the early years of this series the authors had a policy of treating infected aortic grafts either by *in situ* reconstruction or by extra-anatomic reconstruction, depending on the extent of infection seen during exploration. An *in situ* reconstruction was chosen when only a bile stain was found on the prosthesis or when it was considered that limited infection could be treated adequately by local therapy. An extra-anatomic reconstruction was performed when major infection was present. Local adjunctive irrigation systems were never used in this series.

In-hospital patient survival after anatomic and extra-anatomic reconstruction was similar. However, during follow-up patients treated by excision of the aortic prosthesis and an extra-anatomic bypass had a poorer outcome than those treated by *in situ* reconstruction. This was mainly due to rupture of the aortic stump in the former group, probably caused by persistent local infection. Nowadays antibiotic sponge is available for local treatment of infection. Of the ten patients treated by prosthetic resection and left with a blind aortic stump, stump disruption occurred in five with enteric fistula. If only patients who died during operation or during the in-hospital postoperative period are considered, the survival rate in this series was ten of 27. If patients with non-enteric fistula are included, the survival rate was 13 of 31. If patients who died before operation could be performed are excluded, the survival rate was 13 of 25. If only patients who could actually undergo reconstruction are considered, the survival rate was 13 of 20.

In this institution, greater awareness of a possible prosthetic fistula has led to an earlier recognition of the problem and diagnostic investigation. Such awareness may be the most important factor in increasing survival for those with a prosthesis-related fistula. Other series have reported survival rates ranging from 26 to 75 per cent[3–5,29,33,35]. The present results favour *in situ* reconstruction in selected cases, but ultimately the choice of method will depend on the degree of infection found in the vascular bed.

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British Journal of Surgery 1996, 83, 1735–1738

Prospective randomized study of a new method of providing postoperative pain relief following femoropopliteal bypass

J. P. GRIFFITH, S. WHITELEY* and M. J. GOUGH

*Vascular Surgical Unit and *Department of Anaesthetics, The General Infirmary, Great George Street, Leeds LS1 3EX, UK*
Correspondence to: Mr M. J. Gough

The extensive incision required for femoropopliteal bypass using saphenous vein causes significant postoperative pain, principally within the distribution of the cutaneous branches of the femoral nerve. This prospective randomized study investigated the efficacy of continuous postoperative femoral nerve block in reducing both pain (visual analogue pain score) and the requirement for opiate analgesia. Ten patients received a femoral nerve block by infusion of 0·5 per cent bupivacaine (5 ml/h for 48 h) via an epidural catheter together with a patient-controlled analgesia (PCA) device containing morphine; a further ten patients used a PCA device alone. The median postoperative intravenous morphine requirement was significantly reduced in patients with a nerve block at 24 h (4 *versus* 33 mg, $P < 0.01$) and at 48 h (5 *versus* 37 mg, $P < 0.01$) compared with controls. Postoperative pain was effectively abolished in the former group. The addition of a nerve block to PCA provides superior pain control after femoropopliteal bypass.

Peripheral vascular disease presenting with claudication affects 4·5 per cent of the 55–74 years age group[1] and occlusive disease of the superficial femoral artery is responsible for approximately 50 per cent of cases[2]. For patients with disabling claudication or limb-threatening ischaemia, femoropopliteal bypass is a widely used procedure. While autologous saphenous vein is generally considered to be the conduit of choice for infrainguinal reconstruction[3], synthetic grafts may be employed when the saphenous vein is not available. Although harvesting the saphenous vein requires a longer incision, clinical experience suggests that even implantation of synthetic grafts results in significant postoperative pain, which requires opiate analgesia for its control.

The cutaneous nerve supply in the areas of the incisions used for femoropopliteal bypass arises predominantly from branches of the femoral nerve, including the saphenous nerve, with an additional supply from the obturator and genitofemoral nerves. Local anaesthetic techniques, including the three-in-one nerve block first described by Winnie *et al.*[4], have been used to block these nerves successfully for the perioperative and postoperative management of patients undergoing total hip and knee replacement[5,6], resulting in a significant reduction in the requirement for postoperative opiates. Furthermore, no complications arose as a result of the technique. Creton[7] has reported a series of 700 patients who successfully underwent varicose vein surgery using a similar regional block.

With this background, a prospective randomized trial has been performed to evaluate the hypothesis that postoperative analgesia achieved in this way is a safe and effective method of reducing patient analgesic requirements following femoropopliteal reconstruction.

Patients and methods

Twenty consecutive patients undergoing femoropopliteal bypass under general anaesthesia were randomized into one of two groups of equal size. Patients in the control group were given a patient-controlled analgesia (PCA) device (Graesby 3300 pump, Graesby Medical, Watford, UK) after operation, while the study group received a postoperative femoral nerve infusion of local anaesthetic via an infusion catheter and filter (Portex, Hythe, UK) connected to an infusion pump (Medex, Haslingden, UK) in addition to the PCA device. Allergy to local anaesthetics, weight less than 50 kg (risk of anaesthetic toxicity) and groin sepsis were exclusion criteria. Following premedication with temazepam, a standardized anaesthetic technique was used in both groups. The PCA devices contained 50 mg morphine in 50 ml normal saline and were programmed to deliver 1 mg morphine intravenously on patient demand, with a 5-min lockout period between doses. No background infusion was given and PCA use was continued for 48 h after operation.

In patients who were randomized to receive a femoral nerve block, 20 ml 0·25 per cent bupivacaine were injected into the line of the proposed groin incision following induction of anaesthesia. After dissection of the femoral artery a further 20 ml 0·25 per cent bupivacaine was injected under direct vision into the femoral nerve, which may be identified lateral to the artery and its surrounding sheath, in a gutter between the psoas and iliacus muscles. Thereafter, the popliteal artery and saphenous vein were exposed.

After completion of the vascular anastomoses, an 18-Fr epidural catheter was inserted along the femoral nerve, with its tip positioned 5 cm above the inguinal ligament to achieve effective blockade of the cutaneous branches of the femoral, obturator and genitofemoral nerves. To facilitate siting the catheter in the correct position, a small space beneath the inguinal ligament was developed digitally by elevating the iliac fascia (which fuses with the inguinal ligament) from the psoas and iliacus muscles. The wound was then closed, with the catheter brought out through the incision in the upper thigh. The exit site was covered with a sterile occlusive dressing and the infusion pump connected to the catheter via a sterile micropore filter. An infusion of 0·5 per cent bupivacaine at a rate of 5 ml/h was commenced in the recovery room and maintained for 48 h after surgery. The total dose of bupivacaine was below that considered to have risks of toxic side-effects when used for peripheral nerve blockade.

The length of the skin incisions was measured on the third postoperative day and the total dose of morphine supplied by the PCA device calculated. Administration of additional oral analgesia following discontinuation of PCA was also recorded. Finally, all patients completed a visual analogue pain score assessment at 6, 24, 48 and 72 h after surgery

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Paper accepted 21 January 1996

Statistical analysis

Results are expressed as median (interquartile range (i.q r.)). Statistical comparison between the two groups was performed with the Mann–Whitney U test; $P<0{\cdot}05$ was considered statistically significant.

Results

The two groups were well matched for age, sex and weight (*Table 1*). Eighteen patients underwent femoropopliteal bypass surgery for disabling claudication; two patients, who both received a postoperative nerve block, had rest pain before surgery. Although the proportion of saphenous vein to prosthetic graft usage was the same in both groups, all control patients had above-knee bypass grafts while two of the study patients had a below-knee reconstruction. This is reflected by a small difference in the total length of skin incision between the groups. Two patients in the control group experienced complications (graft thrombosis, *Haemophilus influenza* pneumonia) but there was no wound infection or haematoma in either group. Although no formal assessment was made of quadriceps function during the period of local anaesthetic infusion, no significant impairment of mobility was observed.

Postoperative analgesic requirement

Results are shown in *Fig. 1*. Twenty-four hours after operation patients with a nerve block had self-administered a median of 4 (i.q.r. 0–10) mg of intravenous morphine compared with 33 (i.q.r. 18–40) mg in the control group ($P<0{\cdot}01$); similar differences were apparent at 48 h (5 (0–11) *versus* 36 (26–40) mg, $P<0{\cdot}01$). Following discontinuation of PCA, only patients in the control group requested oral dihydrocodeine (45 (i.q.r. 0–90) mg at 72 h, $P<0{\cdot}06$).

Visual analogue pain scores

Results are shown in *Fig. 2*. Patients with a nerve block were essentially pain-free following operation with a median score of 0 (i.q.r. 0–1·5) at 6 h and all scores of 0 thereafter (even after the nerve block was discontinued at 48 h). In contrast, controls experienced significantly greater pain throughout the postoperative period with

Table 1 Characteristics of patients undergoing femoropopliteal bypass

	Controls ($n = 10$)	Femoral nerve block ($n = 10$)
Sex ratio (M:F)	5:5	5:5
Age (years)*	65 (55–69)	65 (62–79)
Weight (kg)*	72·5 (59·0–73·9)	65·0 (61·5–68·9)
Claudication:rest pain	10:0	8:2
Saphenous vein:synthetic graft	4:6	4·6
Above:below knee grafts	10:0	8:2
Total length of incision (cm)*	35 (25–43)	42 (27–43)

*Values are median (interquartile range). Control, patient-controlled analgesia alone; femoral nerve block, nerve block plus patient-controlled analgesia

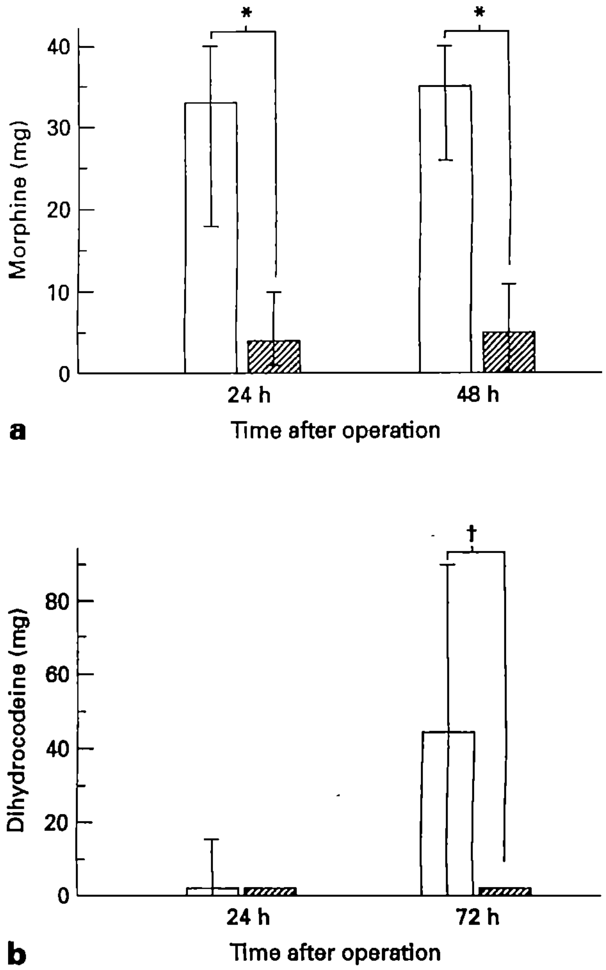

Fig. 1 Postoperative morphine (a) and dihydrocodeine (b) requirements in control (□) and femoral nerve block (▨) groups. Values are median (interquartile range). $^*P<0{\cdot}01$, $^\dagger P<0{\cdot}06$ (Mann–Whitney U test)

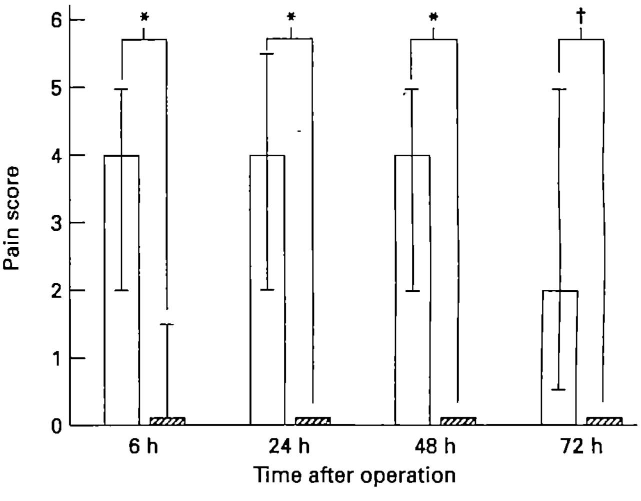

Fig. 2 Postoperative pain scores in control (□) and femoral nerve block (▨) groups. Values are median (interquartile range). $^*P<0{\cdot}01$, $^\dagger P<0{\cdot}05$ (Mann–Whitney U test)

median (i.q.r.) scores of 4 (2–5), 4 (2–5·5), 4 (2–5) and 2 (0·5–5) at 6, 24, 48 and 72 h respectively.

Discussion

The cutaneous nerve supply to the incisions required for femoropopliteal bypass arises from branches of the lumbar plexus which can be blocked by the established technique of a 'three-in-one' block[4]. The authors' experience with the technique is that it is easy to perform, effectively eliminates pain, and significantly reduces the need for opiate analgesia after such surgery. These benefits occurred despite patients in the study group having longer skin incisions than controls and the inclusion of two patients with rest pain in the former group. Similar findings have been reported in patients following knee surgery[6,8] and limb amputation for ischaemia[9]. It has also been suggested that the three-in-one nerve block may prevent the respiratory problems associated with narcotic analgesia following knee surgery in patients with cystic fibrosis[10]. Such a feature might also be helpful in vascular surgical patients who, by virtue of their high prevalence of smoking and chronic respiratory problems, are at considerable risk of postoperative chest complications. While the present study is too small to draw firm conclusions, it is interesting to note that one patient in the control group developed a *Haemophilus* pneumonia, while there were no similar problems in those receiving a nerve block.

The analgesic effect of nerve blockade persisted after removal of the catheter, with pain scores in study patients remaining lower than those in controls at 72 h. This finding is analogous to that of Bach *et al.*[11], who showed that such an infusion reduces initial phantom limb pain in patients undergoing lower limb amputation. A reduction in the afferent painful stimuli to the spinal cord during surgery and in the immediate postoperative period, which produce a state of spinal cord hyperexcitability, is the mechanism by which prolonged pain relief is thought to occur following discontinuation of the nerve block[12,13].

The dose of bupivacaine used in this study was similar to that employed by others[8,10,12]. Its slow absorption from the perineural space, a site of low vascularity, ensures the safety of the technique. Furthermore, positioning the catheter under direct vision avoids any risk of intravascular infusion. A potential hazard of the technique is that the epidural catheter may act as a port of entry for skin organisms and so increase the risk of graft infection. However, some surgeons routinely employ drains following femoropopliteal bypass without apparently incurring an increase in such complications. Despite this, it seems sensible to site the catheter in the lower part of the groin wound and to cover the exit site with a sterile occlusive dressing. Furthermore, the use of an in-line filter and a continuous infusion, rather than intermittent injections, may further reduce the risk of infection.

Perioperative and postoperative epidural anaesthesia must be considered as an alternative to the technique described in this paper. Although epidural anaesthesia has the advantage that it provides anaesthesia for the surgery itself, there are several potential disadvantages. These include a greater requirement for perioperative fluid administration, hypotension and postoperative urinary retention. Furthermore, epidural anaesthesia may be variable in its effect and may be impractical or impossible to perform. Finally, a postoperative epidural infusion requires increased nursing care and usually affects both legs, thereby confining the patient to bed. In contrast, those with a femoral nerve infusion remain pain-free and achieve early mobility, despite the theoretical possibility of producing a significant motor block leading to impaired quadriceps function. The absence of this complication can probably be explained by the differing sensitivity of nerve fibres of varying types to topical local anaesthetic. While the motor branches of the femoral nerve consist of large myelinated $A\alpha$ fibres, pain is mediated by unmyelinated C fibres and the much smaller myelinated $A\delta$ fibres, which are much more sensitive to local anaesthetic[14].

Regional anaesthetic techniques such as femoral nerve blockade may also have other benefits. These include a reduction in peripheral vascular resistance with increased graft flow and amelioration of the detrimental effects of a surgical insult upon the coagulation cascade[15,16]. Christopherson *et al.*[17] have reported that epidural anaesthesia for vascular reconstruction is associated with a lower incidence of early surgical reintervention, although any long-term benefit of regional nerve blocks on graft patency remains unknown.

In summary, this study has demonstrated that continuous femoral nerve blockade is a simple and safe technique which provides excellent postoperative analgesia following femoropopliteal bypass. Its routine use is recommended following infrainguinal reconstruction and further studies examining its influence on coagulation and graft patency would be of interest.

Acknowledgements

The authors wish to thank research nurses, Rhona Hooper and Moira Gough, and the nursing staff of ward 23 at The General Infirmary at Leeds for help with this study.

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British Journal of Surgery 1996, 83, 1739–1740

Case report

Transposition of the anorectum to the abdominal wall

N. S. WILLIAMS, D. G. CORRY, J. F. ABERCROMBIE and J. POWELL-TUCK

Academic Department of Surgery, St Bartholomew's and the Royal London School of Medicine and Dentistry, London, UK
Correspondence to: Professor N S. Williams, Surgical Unit, The Royal London Hospital, London E1 1BB, UK

A unique procedure is described in which the anorectum is mobilized on the inferior mesenteric vascular pedicle and transposed to the anterior abdominal wall. The aim is to preserve maximal intestinal length in patients with short bowel syndrome and intractable diarrhoea. Unique physiological data provided by the second case demonstrate that the specialized sensory functions of the rectum reside in the rectal wall and are subserved by an autonomic nervous supply that is independent of the pudendal nerves.

Case reports

Patient 1

A 58-year-old woman underwent massive small bowel resection for acute intestinal ischaemia. Only 5 cm of small bowel was preserved and a jejunocolic anastomosis was fashioned. After the procedure the patient developed uncontrollable diarrhoea, causing faecal incontinence and severe perianal excoriation.

Patient 2

An 84-year-old woman underwent jejunoileocaecal resection for intestinal infarction. Some 120 cm of healthy small bowel remained. She had severe diarrhoea and faecal incontinence, which rendered her housebound.

Both patients had evidence of intestinal insufficiency requiring enteral and parenteral nutrition. To palliate the diarrhoea of these patients and to preserve as much bowel as possible, a novel procedure employing the anorectum as an abdominal stoma was devised.

Procedure

The rectum was mobilized to the pelvic floor, care being taken to avoid damage to the inferior mesenteric pedicle and its rectal distribution. The anal canal was dissected from the perineum in a fashion similar to the technique of abdominoperineal excision of the rectum but the plane of dissection was close to the external anal sphincter. Internal and external anal sphincters were preserved, although the middle and inferior rectal vessels and the pudendal nerves were inevitably divided. The anal canal was then delivered into the abdominal wound and exteriorized as a left iliac fossa stoma. The anal skin was trimmed around the circumference of the anal canal and was sutured circumferentially to the skin of the abdominal wall.

Patient 1 made an uneventful recovery. The elimination of diarrhoea, incontinence and perianal excoriation resulted in a dramatic improvement in her quality of life. Unfortunately, she died suddenly at home 10 weeks after surgery from myocardial infarction.

Patient 2 also made an uneventful recovery, soon returning to normal life, despite a high stoma output Surprisingly, she reported a feeling of defaecatory desire before the passage of stool into the stoma appliance. She also claimed to be able to distinguish between flatus and stool before its passage.

Physiological measurements

Measurements were made before and 8 weeks after operation in patient 2.

Anal canal manometry. Static station pull-through manometry at 1-cm intervals along the anal canal was performed with a standard water-filled microballoon technique.

Anal canal sensation A mucosal electrosensitivity technique was employed[1]. A 5-Hz 0·1-ms pulse with alternating current was passed between two ring electrodes placed in the anal canal. The sensory threshold was measured 10, 5, 3 and 1 cm from the mucocutaneous junction.

Rectal sensation Rectal sensation was measured by balloon distension of the transposed rectum. A balloon, mounted on a Foley catheter, was introduced into the rectum and then distended at a constant rate (1·3 ml/s) with water at 37°C. The threshold sensory volume, the nature of the sensation and volume of defaecatory desire, and maximum tolerated volume were recorded. Ability to discriminate the nature of rectal contents was tested by introducing porridge, water or air into the rectum via a large catheter. The patient was blinded to the nature of the filling material.

Results

The data obtained from patient 2 are given in *Table 1*. There appeared to be internal sphincter tone following transposition of the anal canal. The trace showed the normal baseline pattern changes in pressure with time. There was complete loss of external sphincter function. Anal canal sensation was also lost. Balloon distension of the rectum provoked sensations of pelvic filling and

Table 1 Physiological data obtained from patient 2 before and 8 weeks after operation

	Before operation	After operation
Anal canal length (cm)	2	3
Maximum resting pressure (cmH_2O)	55	115
Maximum achieved pressure (cmH_2O)	105	115
Mucosal electrosensitivity (mA)		
Distance from anal margin (cm)		
10	16·7	13·5
5	13·3	>25
3	10·0	>25
1	7·5	>25
Rectal sensation (ml)		
Threshold sensory volume	95	120*
Volume of defaecatory desire	160	190†
Maximum tolerated volume	240	220‡

*Abdominal pressure; †pelvic filling; ‡abdominal pain (stop filling)

Paper accepted 18 August 1996

defaecatory desire. Continued distension, past the defaecatory desire point, provoked abdominal pain. The patient was able to discriminate between solid and gaseous rectal contents, but not between liquid and gaseous content.

Discussion

These cases demonstrate the feasibility of bringing the anorectum to the abdominal wall as a stoma. Preservation of the water-absorbing capacity of the anorectum prevented the need for permanent intravenous infusion of fluids, which might have been required if a conventional ileostomy had been constructed in these two patients. This technique may be of potential benefit in patients for whom the retention of intestinal length is of critical importance.

The second patient served as a unique physiological model. After transposition of the anal canal, all somatic nervous supply to the anorectum was destroyed. The destruction of the pudendal nerves would also have resulted in the loss of some parasympathetic innervation. It seems likely that some parasympathetic and sympathetic fibres were retained, reaching the rectum via the hypogastric plexus and the inferior mesenteric pedicle.

The abolition of anal sensation and motor function of the external anal sphincter was unsurprising. However, preservation of the conscious sensation of defaecatory desire on balloon distension of the rectum demonstrates that there must be specialized sensory rectal nerve fibres that reach the central nervous system via the inferior mesenteric pedicle or gut wall.

There has been some debate about the location of the specialized sensors that detect rectal filling. The rectal mucosa, muscular wall and pelvic floor have all been proposed as the site of sensation[2-5]. Recent studies of rectal sensation after coloanal anastomosis, restorative proctocolectomy and total anorectal reconstruction have almost conclusively demonstrated that the pelvic floor is not responsible for sensation of rectal distension[6-9]. This case has clearly shown rectal sensation with no possibility of it originating anywhere but the rectum itself. This proves that the rectum does contain a specialized sensory innervation, which is autonomic.

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British Journal of Surgery 1996, 83, 1741–1743

Prognostic value of negative intraoperative ultrasonography in primary colorectal cancer

M. A. PAUL, J. G. A. M. BLOMJOUS*, M. A. CUESTA and S. MEIJER

*Departments of Surgery and *Radiology, Free University Hospital, PO Box 7057, 1007 MB Amsterdam, The Netherlands*
Correspondence to: Dr M. A. Paul

The risk of developing recurrent tumour was assessed in a group of 85 patients with primary colorectal cancer who had a negative intraoperative ultrasonographic examination at the time of primary tumour resection. At a median follow-up of 40 months liver metastases had developed in 14 patients (16 per cent). Dukes classification of the primary tumours was stage A, B and C in one, three and ten patients respectively. The interval between primary tumour resection and detection of metastases varied from 6 to 24 months but all became evident within 2 years. Sixteen patients (19 per cent) presented with extrahepatic recurrence, one of whom also developed liver metastases. A negative intraoperative ultrasonographic examination did not prove to be a favourable prognostic factor which allowed exclusion from follow-up or adjuvant chemotherapy.

The liver is the most common site of metastases in colorectal cancer[1]. Occult metastases, which escape detection at the time of initial curative surgery, are present in 25 per cent of patients[2]. Intensive postoperative surveillance is carried out to detect these recurrences at an early stage when they may still be resectable. However, resection of liver metastases is possible in only a minority of patients[3] and the value of follow-up programmes is being questioned[4,5]. To minimize recurrence, adjuvant chemotherapy is presently being given to all patients with locally advanced tumours[6]. This strategy, based on the pathological staging system, implies overtreatment of a large number of patients who are likely to be cured by surgery alone, and better methods to assess an individual patient's risk of developing recurrent disease are needed urgently[7]. To identify such high-risk patients, the biological characteristics of the tumour as well as improved liver imaging techniques have been studied. The rationale of the latter approach is that early detection of small liver metastases would potentially allow easier resection, while patients with irresectable disease could be given chemotherapy while the tumour load was still small. Alternatively, if patients with negative liver imaging turn out to have a very low risk for developing recurrent disease, they might be excluded from expensive follow-up schemes or even from adjuvant therapy[8]. At present, the most sensitive imaging technique is intraoperative ultrasonography combined with palpation.

In this study the risk for tumour recurrence and the disease-free interval were assessed in a group of 85 patients with colorectal cancer who had negative ultrasonographic imaging at the time of primary tumour resection.

Patients and methods

Patients

Between December 1989 and December 1992, 124 consecutive patients with primary colorectal cancer were admitted for elective operation. In 26 patients liver metastases were found by palpation and/or intraoperative ultrasonography and one other patient had positive para-aortic lymph nodes. In the remaining 97 patients curative resection was performed. Nine of these 97 patients died after operation. Three more patients died within the next 2 years from non-related causes. Thus, the study comprises 85 patients with negative intraoperative ultrasonographic findings who have been followed for at least 2 years. Patient characteristics are shown in *Table 1*.

Intraoperative ultrasonography

At surgery, the falciform ligament was transected and the liver examined by inspection and bimanual palpation. Subsequently intraoperative ultrasonography was performed by an experienced radiologist, using an Aloka SDD-650 real-time scanner with a 5-MHz linear-array transducer (Aloka, Tokyo, Japan). A 5-MHz transducer was chosen because it combines good definition of metastasis with adequate penetration. A small blind zone is present immediately below the transducer, but possible metastases in this area can usually be detected by palpation. Using this transducer and palpation the sensitivity, specificity and accuracy of intraoperative ultrasonography in this group of patients were 96, 98 and 98 per cent respectively[9]. The transducer was covered by a disposable sterile latex sheath containing acoustic gel. The liver was scanned from both the anterior and posterior surfaces. No stand-off devices were used. Suspicious lesions were subjected to biopsy, unless the patient was scheduled for liver resection. Non-neoplastic lesions were carefully recorded, using Couinaud's segmental numbering, with regard to future ultrasonography during follow-up

Table 1 Characteristics of 85 patients with negative intraoperative ultrasonography of the liver

	n
Sex ratio (M:F)	38:47
Mean (range) age (years)	66 (37–89)
Location of tumour	
Caecum	12
Ascending colon	13
Transverse colon	1
Descending colon	4
Sigmoid colon	31
Rectum	24
Dukes stage	
A	13
B	32
C	40

Paper accepted 23 February 1996

Postoperative assessment

Follow-up at 6-monthly intervals consisted of history taking, physical examination, liver ultrasonography and determination of serum carcinoembryonic antigen (CEA) levels. For ultrasonography the same Aloka scanner was used, but with a 3·5-MHz curved-array transducer. CEA levels were determined with the use of a commercially available assay (Boehringer Mannheim, Mannheim, Germany) using a cut-off level of 5 ng/ml. A lesion was considered to be a metastasis if it appeared *de novo* in conjunction with a rise in serum CEA concentration or was shown to have increased in size by repeated imaging. Follow-up ranged from 24 to 60 (median 40) months. The assessment was incomplete in three elderly patients who did not return to the hospital. Follow-up in these patients consisted of history taking and physical examination only. However, all three were well for more than 3 years after operation.

Results

Liver metastases developed in 14 (16 per cent) of the 85 patients as the first sign of recurrent disease. The interval between primary surgery and detection of the metastases varied from 6 to 36 months. One patient, initially lost to follow-up, presented at 36 months with a large symptomatic liver metastasis 10 cm in diameter. If it is assumed that ultrasonography performed at 24 months would have detected this metastasis, all metastases appeared within 2 years after surgery. In one patient a liver metastasis was detected at 6 months and in three others multiple metastases were found 12 months after operation. Of the 14 patients only three had potentially resectable liver metastases. Two underwent liver resection, including the patient with the metastasis at 6 months' follow-up, but the third patient was found to have concomitant lung metastases. Dukes classification of the primary tumours was stage A in one patient, stage B in three and stage C in ten.

Extrahepatic recurrence developed in 16 patients (19 per cent). Eleven patients presented with a local recurrence, of which two were anastomotic recurrences. One patient underwent re-resection, but was found to have liver metastases 6 months later. Because this patient already had recurrent disease, she is not included in the group with liver metastases. The primary tumours of these 11 patients were staged Dukes A in one, B in five and C in five. The remaining five patients had extrahepatic metastases as the first sign of tumour recurrence. One patient presented with brain and skin metastases, another with lymph node metastases in the groin. Both had had a Dukes stage C tumour in the lower third of the rectum. The remaining three patients had intra-abdominal metastases. Two of them presented with a large ovarian metastasis, requiring laparotomy, at which time both patients also had several small peritoneal deposits. Repeated intraoperative ultrasonography showed no liver metastases. The third patient was found to have large para-aortic lymph node metastases at ultrasonography and subsequent computed tomography. The stage of the primary tumour had been Dukes C in all three patients. The recurrences are summarized in *Table 2*.

All local recurrences and extrahepatic metastases became apparent within 24 months of primary tumour resection. The overall recurrence rate was 15 per cent (two of 13) for Dukes stage A tumours, 25 per cent (eight of 32) for Dukes B and 50 per cent (20 of 40) for Dukes C.

Table 2 Site of recurrence and Dukes stage of primary tumour

	Dukes stage			No. of patients ($n = 85$)
	A	B	C	
Metastases				
Liver	1	3	10	14 (16)
Ovary	0	0	2	2 (2)
Brain	0	0	1	1 (1)
Groin	0	0	1	1 (1)
Para-aortic nodes	0	0	1	1 (1)
Local recurrence	1	5	5	11 (13)
Total	2	8	20	30 (35)

Values in parentheses are percentages

Discussion

Intraoperative ultrasonography is at present the most sensitive liver imaging technique available[10] and can identify lesions with a diameter as small as 5 mm. In liver resection the usefulness of intraoperative ultrasonography has been well documented: additional metastases were found in 25–35 per cent of patients scheduled for metastasectomy[11–13]. Studies in patients with primary colorectal cancer have confirmed the high sensitivity and specificity of intraoperative ultrasonography[9,14–19] and its routine use has been recommended by several authors[14–17,20]. However, as stated by Stone *et al.*[8], routine use of intraoperative ultrasonography is justified only if it changes treatment policy in a large number of patients, by showing either a significant increment in the detection of resectable metastases or a very low false-negative rate, proven through follow-up, allowing patients to be excluded from adjuvant chemotherapy trials or costly follow-up schemes. Most authors recommending routine use of intraoperative ultrasonography in primary colorectal cancer have reported a comparison between imaging techniques lesion by lesion rather than the proportion of patients whose metastases were detected by intraoperative ultrasonography alone[14–17]. However, if only patients with negative preoperative imaging are considered, the yield from intraoperative ultrasonography is much lower and detection rates vary between 3 and 10 per cent. To some authors this proportion is still high enough to recommend the use of intraoperative ultrasonography in all patients, also because it can be performed safely and quickly[14–17,20]. Others have advised against the intraoperative ultrasonography when preoperative imaging is normal, either because the yield was low with some false-positive results[8,9] or because duplex Doppler ultrasonography with measurement of the Doppler perfusion index was found to be superior to intraoperative ultrasonography[21]. Selective use of intraoperative ultrasonography in patients at high risk (e.g. with T_3 tumours) may be more cost effective[8], but the stage of the primary tumour is seldom known before operation. Whatever the recommendations, the detection rates in patients with negative preoperative imaging seem to indicate that only a minority of occult liver metastases are detectable by intraoperative ultrasonography.

Follow-up data after intraoperative ultrasonography imaging have, therefore, been awaited with interest. If patients with a negative intraoperative ultrasonographic finding prove to be at very low risk for tumour recurrence, this would influence the design of follow-up programmes

Table 3 Incidence of liver metastases in patients with negative intraoperative ultrasonography at primary tumour resection

Reference	Tumour type*	No. of patients	Metastases (%)	Follow-up (months)
Russo *et al.*[15]	pCRC, rec	70	3·4	6–24
Machi *et al.*[17]	pCRC	189	6·9	37
Leen *et al.*[21]	pCRC	90	21	12
Stone *et al.*[8]	pCRC, rec	56	17	23
Present study	pCRC	85	16	40

*pCRC, primary colorectal cancer; rec, recurrent colorectal cancer

and adjuvant chemotherapy trials. Initial reports about the negative predictive value of intraoperative ultrasonography were favourable. Russo *et al.*[15] reported a recurrence rate of 3·4 per cent at 6–24 months' follow-up, and in the large series of Machi *et al.*[17] only 6·9 per cent of patients had developed liver metastases at a median follow-up of 37 months. However, the latter study also included patients with known metastases. When only patients with negative intraoperative ultrasonographic findings at operation were considered, metastatic disease occurred in 9 per cent (13 of 144) of the patients. In two more recent studies[8,21] liver metastasis occurred in 13 and 21 per cent of patients with negative findings. The present study also shows a 16 per cent recurrence rate in the liver (*Table 3*). The difference in outcome might be explained by a possible difference in the number of patients with advanced tumours.

In general, recurrence rates of 15–20 per cent should occur if a detection rate of 5–10 per cent by intraoperative ultrasonography and a prevalence of occult metastasis of approximately 25 per cent in older historical studies are considered. The most likely explanation for this failure of intraoperative ultrasonography to detect most of the occult metastases is the size of the lesions at the time of liver imaging. Presumably the majority of metastases that become clinically evident within 6–24 months were very small at the time of primary tumour resection.

Eleven of the present patients presented with true local recurrence. In the literature such recurrences are often associated with dissemination[22]. However, none of these 11 patients was found to have liver metastases at liver imaging, although one had so 6 months later.

When both intrahepatic and extrahepatic recurrences are considered together, the recurrence rate for Dukes stage B and C tumours was still 25 and 50 per cent respectively, indicating the need for adjuvant therapy following tumour resection.

In conclusion, these data do not support the exclusion of patients with negative intraoperative ultrasonographic imaging from either follow-up schemes or adjuvant chemotherapy.

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British Journal of Surgery 1996, 83, 1744–1746

Ambulatory manometric examination in patients with a colonic J pouch and in normal controls

J. ROMANOS, J. F. STEBBING, M. M. SMILGIN HUMPHREYS,
N. TAKEUCHI and N. J. McC. MORTENSEN

Department of Colorectal Surgery, John Radcliffe Hospital, Oxford OX3 9DU, UK
Correspondence to: Mr N. J. McC. Mortensen

Anorectal function after anterior resection may be impaired as a result of reduced luminal capacity in the pelvis. The aim of this study was to evaluate the colonic J pouch neorectum by means of ambulatory manometry. Twelve patients with a colonic pouch following anterior resection and seven healthy controls were studied for a median of 6 (range 6–24) h using a probe with two pouch–rectal and two anal canal transducers. Records were interpreted by visual inspection. Pressure values and wave frequencies were determined by software analysis. Pouches had been functioning for a median of 32 (range 11–55) months. All patients with a pouch had an acceptable stool frequency. Seven of 12 patients complained of incomplete evacuation. Resting anal canal pressure (73 *versus* 100 cmH$_2$O), pouch–rectal pressure (29 *versus* 15 cmH$_2$O) and anal canal pouch–rectal pressure gradients (60 *versus* 85 cmH$_2$O) were similar in patients and controls. The frequency of slow-wave activity in patients with a pouch was significantly lower than that in controls (7 *versus* 16 cycles per min, $P = 0{\cdot}001$). Coordination between the colonic J pouch and the anal canal, in the form of sampling episodes, was observed in more than half of the patients with a functioning pouch. Large isolated contractions (pressure greater than 30 cmH$_2$O and lasting longer than 20 s) and rhythmic contractions were the most frequent pattern of pouch motility.

Sphincter-saving operations are now widely accepted in the treatment of tumours of the middle and lower third of the rectum. Ultra-low anterior resection is associated with functional problems of increased frequency, urgency, incontinence and nocturnal seepage, at least in the early postoperative period[1]. These problems are thought, in part, to result from loss of the normal reservoir function of the rectum[1,2]. Use of a colonic J pouch to create a neorectal reservoir is a relatively new technique, first described in 1986[3,4], which aims to avoid the symptoms of 'anterior resection syndrome'[5]. Several studies have evaluated the functional results of the colonic J pouch, with promising results[6–9]. However, there are no published reports of ambulatory manometric examination of the colonic J pouch.

The aim of this study was to compare the anal canal pressure, pouch–rectal pressure and anal pouch–rectal pressure gradient in patients with a colonic pouch and in normal controls, and at the same time to record the motility pattern of the colonic pouch and its coordination with anal motor activity over prolonged recording periods and to relate this to functional outcome.

Patients and methods

Twelve patients (8 men; median age 62 (range 43–71) years) who underwent low anterior resection with colonic J pouch–anal anastomosis between June 1990 and September 1994, and seven healthy control subjects (5 men; age 40 (range 33–50) years) were studied. Diagnosis of carcinoma of the rectum was confirmed in 11 patients (Dukes' stage A, six patients; stage B, three patients; stage C, two). One patient had radiation proctitis.

Operative technique

Patients were operated on by one surgeon (N.J.McC.M.) with high ligation of the inferior mesenteric artery, a no-touch technique and total mesorectal excision. The splenic flexure was routinely mobilized and a colonic J pouch, with 9-cm limbs, was fashioned from the descending colon using one firing of a linear GIA 90 (AutoSuture, Ascot, UK) stapler, introduced through a small colotomy. A stapled pouch–anal anastomosis was performed at a median of 3 (range 2·0–4·5) cm from the anal verge. All patients had a covering loop ileostomy.

Ambulatory manometry

Informed written consent was obtained from all subjects before examination and the study was approved by the ethics committee

Continuous ambulatory manometry was performed with the Gaeltec 7-MPR system with 1 MB memory (Gaeltec, Isle of Skye, UK). This is a 188 × 137 × 45-mm box, weighing 650 g and operated by four AA size alkaline batteries which are sufficient to power the recorder for at least 24 h. A 2-mm diameter, soft, flexible probe with microtransducers mounted at the tip and at 4, 12 and 13 cm was connected to the recorder and calibrated (positive-pressure method) before each recording. Pressures were measured in centimetres of water. No bowel preparation was undertaken and all recordings were started in the morning.

The subject was placed in the left lateral position and the probe was inserted into the rectum or pouch. At set-up, real-time display of the recording on a personal computer allowed accurate positioning of the proximal microtransducers in the upper and lower anal canal. The probe was secured by Sleek (Setonplast, Smith and Nephew Healthcare, Kingston upon Hull, UK) tape applied from the anal verge around to the buttocks, which ensured a steady position of the probe throughout the recording. A final testing of the probe position was performed and the device was disconnected from the real-time display and connected to the portable recorder.

The recorder was readily worn on the shoulder and subjects were able to move freely around the hospital site. Subjects were asked to keep a log book of significant events (sitting, walking, eating, passing urine, feeling and passing wind or faeces) that

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Presented in part to the British Society of Gastroenterology in Warwick, UK, September 1995 and published in abstract form as *Gut* 1995, 37 (Suppl 2): A47
Paper accepted 27 February 1996

occurred during the examination period and simultaneously to press an event button on the recorder to mark the trace.

The record was downloaded to a personal computer for subsequent analysis. All traces were interpreted by one author (J.R.) by visual inspection of the recording, aided by the log books. The mean, maximum and minimum pressure values, and the identification and frequency of waves, were determined by software analysis (Ambulatory Recording System (Type MPR/2); Gaeltec Software, Gaeltec).

For patients with a colonic J pouch a standard questionnaire was used to obtain data concerning the function of the pouch (daytime and nocturnal bowel movements, episodes of incontinence or leakage, evacuation difficulties, use of antidiarrhoeal agents), bladder and sexual function.

Data are expressed as median (range) values. Statistical analysis was performed with Student's t test and $P < 0.05$ was considered significant.

Results

At the time of examination a functioning pouch had been present for a median of 32 (range 11–55) months.

Clinical outcome

Details of the clinical outcome in patients with a colonic pouch are shown in *Table 1*. Four patients reported infrequent episodes of minor incontinence readily managed with small pads. Seven of the 12 patients complained of a sensation of incomplete evacuation but none needed regular use of enemas or laxatives. Four patients experienced occasional difficulty in evacuation but did not require any active treatment.

Ambulatory manometry

The duration of recording was 6 (range 6–24) h. The probe was well tolerated by the subjects. In two patients, the probe was expelled during a bowel action and had to be reinserted.

Analysis over the whole recording period showed that there was no significant difference between patients and controls in mean resting anal pressures (J pouch 73 (44–118) *versus* controls 100 (45–120) cmH_2O) and pouch–rectal pressures (29 (4–74) *versus* 15 (5–25) cmH_2O). The anal canal pouch–rectal pressure gradient was similar in patients and controls (60 (4–114) *versus* 85 (32–100) cmH_2O). In the pouch group, incontinent patients had a lower pressure gradient than continent patients (39 *versus* 63 cmH_2O, $P = 0.03$).

Slow-wave activity in the anal sphincter was present in ten of 12 patients and in all controls. The frequency of slow waves in patients with a pouch was significantly lower than that in controls (7 *versus* 16 cycles per min, $P = 0.001$). Sampling episodes (*Fig. 1*) were seen in seven patients. In two patients spontaneous anal relaxation with a reversed pressure gradient was seen and was associated with event-marked episodes of minor incontinence (*Fig. 2*). Large contractions (pressure greater than 30 cmH_2O and lasting longer than 20 s) were seen in ten patients, seven of whom complained of incomplete evacuation. These contractions tended to be more frequent as defaecation approached and to persist after pouch emptying in patients who reported incomplete evacuation (*Fig. 3*). Rhythmic contractions with no consistent pattern were seen in seven patients.

Table 1 Clinical outcome in 12 patients with a colonic pouch

	n
Median (range) stool frequency	
Day	3 (1–6)
Night	0 (0–2·5)
Continence	
Ability to defer evacuation	6
Soiling	4
Discrimination between flatus and solid	12
Antidiarrhoeal agents used	6
Difficulty in evacuation	4
Incomplete evacuation	7
Sexual dysfunction	1
Urinary dysfunction	1

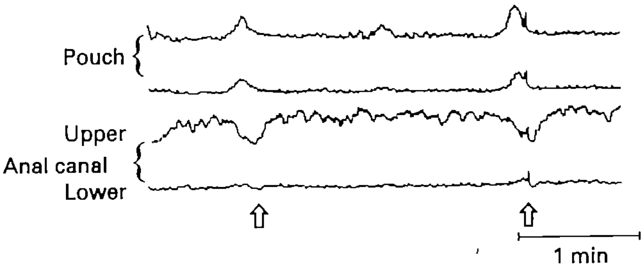

Fig. 1 Sampling episodes (arrows) demonstrate coordination between the colonic J pouch and the anal canal. The external anal sphincter contracts (lower anal canal, right arrow) to help preserve continence

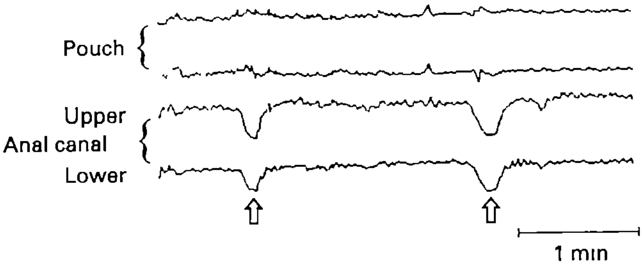

Fig. 2 Two patients showed spontaneous anal relaxation (arrows) throughout the entire length of the anal canal which was associated with faecal seepage

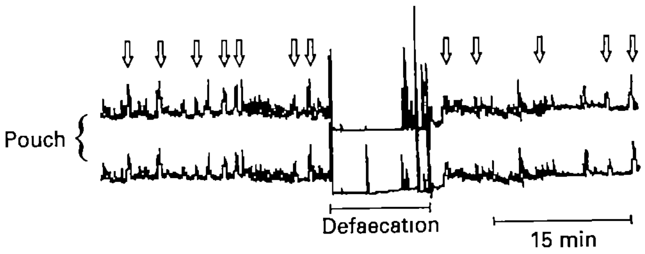

Fig. 3 Large pouch contractions (arrows) that persist after defaecation in a patient complaining of incomplete evacuation. Anal canal traces are omitted for clarity

Discussion

Ambulatory manometry allows evaluation of gastrointestinal motility patterns by continuous measurement of various parameters over a sustained period. Ambulatory studies resemble more closely the normal state and avoid some of the problems associated with static manometry performed in the highly artificial environment of an anorectal physiology laboratory. The use of ambulatory recordings has been advocated by several authors and the results are reproducible and accurate[10–12]. The combination of several microtransducers allows the recording of related events such as sampling episodes or migration of waves through the gastrointestinal tract.

Using ambulatory manometry Williamson *et al.*[13] argued that a decrease in the anorectal pressure gradient was, in part, responsible for the inferior functional results of low anterior resection and suggested that patients with particularly low tumours may benefit from a colonic pouch. In the present study, it was shown that, in patients with a colonic J pouch, the anal–pouch pressure gradient was preserved and remained similar to the anorectal pressure gradient in normal controls. It seems likely that this results from replacement of the rectum by a low pressure reservoir.

Anal canal slow-wave activity was seen in the majority (ten of 12) of patients with a pouch and in all controls, suggesting that stapled pouch–anal anastomosis preserves intrinsic anal sphincter activity. This differs from the study by Williamson *et al.*[13] in which only 50 per cent of patients undergoing straight coloanal anastomosis showed such activity. The effect of anal canal instrumentation on spontaneous myogenic function and the intrinsic nerves is uncertain but may explain the finding of a lower slow-wave frequency in the pouch group. Further studies with the aid of electromyographic recordings may elucidate this finding.

Sampling episodes, where the rectal pressure rises and the upper anal canal pressure falls simultaneously to a similar value, permit discrimination of rectal contents and are a normal finding in controls. They have also been described in patients after coloanal anastomosis and restorative proctocolectomy where the postulated mechanism was regeneration of intramural nerve pathways[14–16]. In the present study coordination between the colonic J pouch and the anal canal, in the form of sampling episodes, was observed in more than half of the patients with a functioning pouch.

Sarna[17,18] described three types of colonic contraction: individual phasic contractions, the basic unit of contractile activity; an organized group of contractions; and special propulsive contractions, first described by Narducci *et al.*[19]. This activity is controlled by myogenic, neural and chemical mechanisms[17], the integrity of which is required for normal function. The colonic J pouch is not just a simple transplant of descending colon into the pelvis. One limb of the pouch is antiperistaltic and at least part of the extrinsic nerve supply is interrupted as a result of high ligation. Waves recorded from a J pouch may therefore not correlate fully with the motor activity of normal descending colon. In addition, interpretation of ambulatory recording of colonic activity is influenced by the length of recording, the number and location of microtransducers and the use of different analysis procedures[18]. In this study the J pouch exhibited a motility pattern that could be classified as long-duration individual phasic and rhythmic contractions according to the frequency, duration and height of the contractions This pattern was recorded mainly from patients with incomplete evacuation and could be explained either by the presence of residual pouch contents, by gradual pouch filling or by a primary abnormality of the malfunctioning pouch.

Acknowledgements

The authors are most grateful to Mr Graeme Duthie for invaluable help with the ambulatory technique and interpretation of the recordings.

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British Journal of Surgery 1996, 83, 1747–1749

Clinical significance of the tumour capsule in the treatment of parotid pleomorphic adenomas

M. McGURK, A. RENEHAN*, E. N. GLEAVE* and B. D. HANCOCK†

*Salivary Gland Service, Department of Oral and Maxillofacial Surgery, UMDS, Guy's Hospital, London, *University Department of Surgery, University Hospital of South Manchester and Christie Hospital, Manchester and †Department of General Surgery, Wythenshawe Hospital, Manchester, UK*

Correspondence to: Professor M. McGurk, Department of Oral and Maxillofacial Surgery, Floor 24 Guy's Tower, Guy's Hospital, London Bridge, London SE1 9RT, UK

The propensity of pleomorphic adenomas to recur is generally attributed to the biological nature of the tumour, and surgery close to the capsule is perceived as undesirable. At the Christie Hospital, Manchester, between 1947 and 1992, 475 tumours arising within the superficial portion of the parotid gland were treated by two surgical techniques: extracapsular dissection (380 patients) and superficial parotidectomy (95). Recurrence rates were 2 per cent in each group (median follow-up 12·5 years). Contact of the tumour with the facial nerve was recorded in 51 per cent of patients. There was no difference between the treatment groups in the incidence of permanent facial nerve injury (2 *versus* 1 per cent respectively). This study demonstrates that dissection in close proximity to the tumour is possible without inducing recurrence and that in practice the microinvasion of the capsule by tumour buds has limited clinical significance.

Pleomorphic adenoma accounts for 60–70 per cent of all neoplasms[1–4] in the parotid gland with an incidence of approximately 1·4 per 100 000 population[5]. Its propensity to recur is generally acknowledged and historically has been attributed to the biological nature of the tumour. In the 1930s, McFarland[6] drew attention to the high incidence of recurrence associated with enucleation and this was subsequently explained in pathological terms by Patey and Thackray[7], who demonstrated a lack of capsular integrity and microscopic extensions of adenoma outside the main body of tumour. Surgery close to the capsule is therefore perceived as undesirable, running the risk of rupture or dislocation and subsequent recurrence. Wide dissection in the form of superficial parotidectomy became the recognized standard treatment[8].

At the Christie Hospital, Manchester, a particular interest in parotid surgery was shown by two surgeons (the late Mr W. A. B. Nicholson and Mr E. N. Gleave), consecutively spanning 45 years. The former surgeon's interest in this tumour, then known as mixed salivary tumour, preceded the work of Patey and Thackray. He developed and practised a local capsular dissection technique which did not accord with the opinion of the greater body of surgeons and continued essentially unchanged for almost half a century. Aspects of this technique have been reported[9]. This paper analyses the results of treatment of pleomorphic adenomas of the parotid gland by extracapsular dissection and compares them with conventional surgery – superficial parotidectomy.

Patients and methods

Between 1947 and 1992, 864 patients with previously untreated epithelial neoplasms (benign and malignant) of the parotid gland were referred for treatment, of which 551 (64 per cent) had a histological diagnosis of pleomorphic adenoma. The median age of this group was 47 (range 5–87) years with a female predominance of 1·6.1 (344 female and 207 male patients) The majority of the surgery was undertaken by two surgeons and the median follow-up was 12·5 (range 1–34) years.

To provide a clear uncomplicated dataset for analysis, 57 patients treated with adjuvant radiotherapy were excluded from the analysis, as were a further 19 with deep lobe tumours or who required partial or total nerve sacrifice. Some 475 patients had primary tumours limited to the superficial part of the parotid gland treated by surgery alone. Two surgical techniques were employed: extracapsular dissection (380 patients) and superficial parotidectomy (95). The former has been described previously[9,10] and involves a meticulous dissection in the filamentous areolar space that surrounds the tumour. Careful haemostasis is esential for the practice of this technique. The decision as to which technique was chosen was made at the time of surgical exploration after the preauricular skin flap was raised. Features favouring extracapsular dissection were mobility of tumour within the parotid and a thin covering of the tumour by glandular tissue

Statistical analysis

Comparison between groups was made using χ^2 analysis and Fisher's exact test where expected frequencies were less than five.

Results

There were nine recurrences, seven following extracapsular dissection (2 per cent) and two after superficial parotidectomy (2 per cent); the median time to recurrence was 59 (range 6–252) months. The theoretical possibility of removing the adenoma with an adequate margin of normal tissue was tested in 408 patients by recording the anatomical relationship of tumour to the facial nerve (*Table 1*). Categorization was based on surgical observations, not histological findings.

The complications encountered with the two techniques are shown in *Table 2*. Extracapsular dissection was associated with a significantly reduced incidence of transient facial nerve damage compared with superficial parotidectomy. The incidence of permanent injury was low and no significant difference was noted between the

Paper accepted 14 March 1996

Table 1 Relationship of tumour to VII nerve*

	No. of patients
I No contact of tumour with nerve	199 (49)
II Tangential contact of tumour with nerve	47 (12)
III Contact for considerable length of nerve	162 (40)

Values in parentheses are percentages. *Classification based on the operation notes of 408 patients

Table 2 Complications by type of surgery

	Extracapsular dissection (*n* = 380)	Superficial parotidectomy (*n* = 95)	*P**
Facial palsy			
Transient	41 (11)	30 (32)	<0·0001
Permanent	7 (2)	1 (1)	n.s.
Frey's syndrome	18 (5)	36 (38)	<0·0001
Amputation neuroma	12 (3)	18 (19)	<0·0001
Salivary fistula	3 (1)	0 (0)	

Values in parentheses are percentages. n.s., Not significant. *χ^2 and Fisher's exact tests

two surgical approaches. Frey's syndrome was much reduced after extracapsular dissection.

Discussion

This study demonstrates that careful dissection in close proximity to a pleomorphic adenoma need not lead to a high incidence of recurrence and that in practice the microinvasion of the capsule by tumour buds has limited clinical significance. This challenges conventional teaching proposed by Patey and Thackray[7] and the implication is that parotid surgery for pleomorphic adenomas is operator-sensitive. In the present series, the majority of surgery was undertaken by two surgeons with extensive experience, which probably accounts for the results achieved. The risk of recurrence is greater following treatment by the occasional parotid surgeon[5].

Analysis in this study was limited to tumours arising within the superficial portion of the gland, thus accounting for some 90 per cent of parotid pleomorphic adenomas. The recurrence rate with long-term follow-up was 2 per cent for both extracapsular dissection and superficial parotidectomy, which compares favourably with that in other series[2,11–13] (*Table 3*). A recent study from Oslo[14] suggests that the rate of recurrence probably increases slightly (2·5 per cent) when minimum follow-up is greater than 10 years.

Extracapsular dissection is an alternative, perhaps less well known, technique of surgical removal of parotid tumours which some advocates of superficial parotidectomy wrongly categorize as enucleation[15]. Rather, it is the careful dissection of the tumour outside the capsule, without prior identification of the facial nerve. Its use has been reported elsewhere but numbers have generally been small[16,17]. The facial nerve is in contact with the tumour capsule in about half the patients and, therefore, conventional parotidectomy frequently embodies the principle of extracapsular dissection without apparent increased risk of recurrence. The lack of correlation between capsular exposure and tumour recurrence has been noted by others[18,19].

Table 3 Reported series of treated pleomorphic adenomas with recurrence rates

Reference	Year	No. of patients	Recurrence rate (%)	Comment
Superficial parotidectomy				
Richardson *et al.*[11]	1975	90	1	All had a minimum follow-up of 5 years
Woods *et al.*[2]	1977	360	2	Follow-up not stated
Steven and Hobsley[12]	1982	72	0	Only 25 per cent had more than 5 years' follow-up
Maynard[13]	1988	130	0·8	65 per cent had more than 5 years' follow-up
Natvig and Soberg[14]	1994	238	2·5	Very long follow-up (11–25 years)
Extracapsular dissection				
Anderson[16]	1975	131	1·5	Over half had more than 5 years' follow-up
Prichard *et al.*[17]	1992	31	0	Median follow-up 46 months
Present study				
Extracapsular dissection		380	2	
Superficial parotidectomy		95	2	Median follow-up 12·5 years

The authors recognize that the two groups in the study were not strictly comparable. Tumours treated by superficial parotidectomy tended to be more deeply placed and this probably explains the higher incidence of neuropraxia. The incidence of permanent injury to the facial nerve was low and there was no difference between the two surgical techniques despite the nerve not being exposed in extracapsular dissection. Compared with other series[2,13], the incidence of Frey's syndrome following superficial parotidectomy was high. This is explained by the long follow-up period: 35 per cent of patients who developed Frey's syndrome (irrespective of surgical technique) first complained of symptoms more than 5 years after initial surgery. Frey's syndrome occurred less often following extracapsular dissection, presumably because of the limited disruption of the parotid tissue rather than the wide exposure of the gland, as a large preauricular flap was raised in both methods.

This study does not recommend extracapsular dissection as a standard technique. The procedure is technically demanding; a substantial part of the practice of the two surgeons in this series was limited to parotid surgery. Superficial parotidectomy is a preferred technique for general application and allows a greater margin for error. The merit of the study is that it relieves the tumour of responsibility for recurrence and focuses attention on surgical technique.

Acknowledgements

The authors thank Messrs O. A. Shaheen, J. D. Maynard and R. G. Williams and Emeritus Professor M. Hobsley for critical appraisal of this manuscript.

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British Journal of Surgery 1996, 83, 1750–1754

Long-term follow-up of over 1000 patients with salivary gland tumours treated in a single centre

A. RENEHAN, E. N. GLEAVE, B. D. HANCOCK*, P. SMITH† and M. McGURK‡

*University Department of Surgery, University Hospital of South Manchester and Christie Hospital and *Department of General Surgery, Wythenshawe Hospital, Manchester, and †Imperial Cancer Research Fund, Clinical Oncology Unit and ‡Salivary Gland Service, Department of Oral and Maxillofacial Surgery, United Medical and Dental Schools, Guy's Hospital, London, UK*

Correspondence to: Professor M. McGurk, Department of Oral and Maxillofacial Surgery, Floor 24 Guy's Tower, Guy's Hospital, London Bridge, London SE1 9RT, UK

Between 1947 and 1992, 1403 patients with 1432 salivary gland tumours were treated at the Christie Hospital, Manchester. There were 1194 epithelial neoplasms: parotid, 1082 (91 per cent); submandibular, 47 (4 per cent); minor glands, 65 (5 per cent). The commonest histological diagnoses were pleomorphic adenoma ($n = 776$) and adenolymphoma ($n = 159$). A total of 244 carcinomas were seen (adenoid cystic carcinoma, $n = 75$). Treatment was primarily surgical, conservative where possible, and determined by tumour extent and not histology. Adjuvant radiation therapy was used in over half the definitively treated malignancies. The recurrence rate following the treatment of 551 new parotid pleomorphic adenomas was 1·6 per cent at median follow-up 12·5 (range 1–34) years, increasing to 15 per cent in the secondarily referred group ($n = 170$). For patients with definitively treated primary salivary carcinomas ($n = 148$), the disease-free survival rate at 5, 10 and 15 years was 58, 47 and 45 per cent respectively. Using multivariate analysis, clinical stage was the most important predictor of survival; the 10-year survival rate for stages I–IV was 96, 70, 47 and 19 per cent respectively.

Tumours of salivary origin arise from the major (parotid, submandibular and sublingual) and minor glands of the upper aerodigestive tract. The overall incidence of benign and malignant salivary tumours is unknown. Malignant disease of the major glands is reported to be 0·7 per 100 000 population[1], whereas minor salivary gland carcinomas are normally classified together with other malignancies at various anatomical sites. Gunn and Parrott[2] collected figures for all new parotid tumours operated on in the north-east of England over a 5-year period, and reported an incidence of 2·4 per 100 000 population. With the exception of a few institutions, experience in the treatment of these tumours is limited. This paper reports on a large series treated at a single centre with long-term follow-up. It updates previously published data[3,4] and aims to provide a valuable baseline against which future studies may be judged.

Patients and methods

Between 1947 and 1992, 1403 patients with 1432 salivary gland tumours were treated primarily by surgery at the Christie Hospital, Manchester, with a minority (approximately 10 per cent) attending at University Hospital of South Manchester. The surgery was undertaken mainly by two surgeons consecutively (the late Mr W. A. B. Nicholson and E.N.G.). Some 1194 tumours were of epithelial origin and are the subject of this study. Other tumours included within the World Health Organization (WHO) classification[5] but excluded from this analysis were: 45 mesenchymal tumours, 49 malignant lymphomas, 29 metastatic tumours and 115 tumour-like lesions (sialosis, lymphoepithelial disease, cysts).

Table 1 shows the distribution of tumours by site. Within the parotid gland, the anatomical distribution of new tumours was: infra-auricular portion of superficial lobe, 75 per cent; preauricular portion of superficial lobe, 12 per cent; deep lobe, 6 per cent; involvement of the whole gland, 5 per cent and accessory lobe, 2 per cent. Minor gland tumours were all within the oral and oropharyngeal areas, with the palate as the most frequent site ($n = 27$, 42 per cent). As sublingual gland tumours were often indistinguishable from those arising from the floor of mouth, they were grouped together with minor salivary gland tumours.

Clinical and pathological findings

Histological classification of tumours was reviewed in the mid-1970s and updated in line with the WHO classifications[5,6]. *Fig. 1* shows the age distribution at initial presentation categorized into the three most common tumour types. A total of 950 patients with benign neoplasms were referred. Pleomorphic adenoma was reported in 776 patients (new, 594; secondary referral, 182) and accounted for 63 per cent of new epithelial neoplasms. Adenolymphoma (Warthin's tumour) numbered 159 tumours in 145 patients; it was multifocal within the same gland in 14 patients and occurred bilaterally in 14. Adenoma usually presented as an asymptomatic mass but in one patient pleomorphic adenoma was associated with a facial palsy, which resolved following surgery. Pain was the presenting feature in three patients with pleomorphic adenoma.

A total of 244 malignant salivary neoplasms (new, 175; secondary referral, 69) were seen, the commonest being adenoid cystic carcinoma (*Table 2*). Pain was the presenting symptom in

Table 1 Site of origin and referral status

	New	Secondary	Total
Parotid			
Benign	722 (84)	170 (78)	1082 (91)
Malignant	141 (16)	49 (22)	
Submandibular			
Benign	21 (66)	6 (40)	47 (4)
Malignant	11 (34)	9 (60)	
Minor			
Benign	25 (52)	6 (35)	65 (5)
Malignant	23 (48)	11 (65)	
Total	943 (79)	251 (21)	1194 (100)

Values in parentheses are percentages

Paper accepted 24 February 1996

Table 2 Distribution of different histological types by anatomical site

	Parotid	Submandibular	Minor	Total
Benign tumours				
Pleomorphic adenoma	721	27	28	776 (65)
Adenolymphoma	159	0	0	159 (13)
Monomorphic adenoma*	12	0	3	15 (1)
Total	892	27	31	950 (80)
Malignant tumours				
Adenoid cystic carcinoma	43	10	22	75 (6)
Mucoepidermoid carcinoma				
Low grade	28	0	7	38 (3)
High grade	3	0	0	
Undifferentiated carcinoma	34	2	2	38 (3)
Adenocarcinoma†	28	2	1	31 (3)
Malignant mixed tumour	21	2	1	24 (2)
Acinic cell carcinoma	20	1	1	22 (2)
Squamous cell carcinoma	13	2	0	15 (1)
Epithelial–myoepithelial carcinoma	0	1	0	1 (0)
Total	190	20	34	244 (20)
Total	1082 (91)	47 (4)	65 (5)	1194 (100)

Values in parentheses are percentages. *Includes oncocytoma and basal cell adenoma; †includes basal cell adenocarcinoma, papillary cystadenocarcinoma, mucinous adenocarcinoma and adenocarcinoma, not otherwise specified

25 per cent and facial palsy in 18 per cent of primary parotid carcinomas ($n = 141$). Approximately half this group had advanced disease on referral and the diagnosis was clinically obvious but 55 per cent presented with an asymptomatic mass. Primary submandibular gland malignancy was uncommon ($n = 11$). Minor gland carcinoma ($n = 23$) occurred in different locations and presented with an asymptomatic mass (48 per cent), pain (13 per cent) and difficulty wearing dentures (17 per cent). Clinically evident invasion of the maxilla and mandible was present in six patients

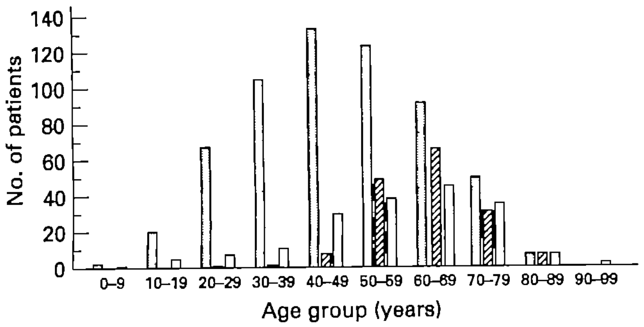


Fig. 1 Age distribution of patients with the three main tumour types: □, pleomorphic adenoma ($n = 594$, sex ratio (M:F) 1:1·6, median age 47 (range 5–87) years); ▨, adenolymphoma ($n = 145$, sex ratio (M·F) 2·2·1, median age 63 (range 29–85) years); □, carcinoma ($n = 175$, sex ratio (M:F) 1·1:1, median age 59 (range 9–92) years)

Table 3 Clinical stage (American Joint Committee on Cancer) at initial presentation by anatomical site

Stage	Parotid	Submandibular	Minor
I	32 (24)	0	4
II	37 (27)	3	11
III	25 (18)	2	2
IV	42 (31)	6	4
Total	136 (100)*	11	21*

Values in parentheses are percentages. *There was insufficient clinical information for staging of five parotid and two minor gland carcinomas

Malignant tumours were staged retrospectively in accordance with the American Joint Committee on Cancer criteria[7] and are shown for the main anatomical sites in *Table 3*. Cervical lymph node metastasis was uncommon at initial presentation (parotid, 18; submandibular, four; minor glands, none) but, where present, there was good correlation with increasing tumour size (T_1, 0 per cent; T_2, 3 per cent; T_3, 17 per cent; T_4, 34 per cent)

Treatment

For the 551 new parotid pleomorphic adenomas, treatment modalities were: local surgery and radium implants before 1956 ($n = 35$); thereafter adjuvant radiotherapy was given to an additional 19 patients because of spillage or rupture, and the remaining 497 were treated by surgery alone Sacrifice of the facial nerve was necessary in six patients (partial, five; nerve trunk, one). Parotid adenolymphomas ($n = 159$) and monomorphic adenomas ($n = 12$) required surgery only. Benign tumours of the submandibular gland ($n = 21$) were treated by complete removal of the gland, whereas minor salivary gland benign tumours ($n = 25$) were treated predominantly by limited resection, a more radical procedure (hemimaxillectomy) being required in four patients.

Benign tumours referred secondarily with residual and recurrent disease (parotid, 170; submandibular, six, minor glands, six) were a heterogeneous group and treatment was determined by a number of factors, including type of previous treatment and extent of tumour. Adjuvant radiotherapy was commonly used, especially for multinodular recurrence.

The treatment protocols for malignant tumours were surgery with or without adjuvant radiotherapy, or radical radiotherapy alone (*Table 4*). Chemotherapy was used only in those with recurrent disease. The magnitude of surgery was determined by the extent of the tumour and not its histological classification. The integrity of the facial nerve was preserved wherever possible. Neck dissection was undertaken in conjunction with primary surgery only when clinically palpable nodes were present. Postoperative adjuvant radiotherapy was the rule for advanced carcinomas (T_3, T_4) and for early disease (T_1, T_2) with high grade, spillage or positive margins. Radical radiotherapy alone was used early in the series, in patients with irresectable tumours and those unfit for surgery. An additional 27 patients with new cancers were treated palliatively.

Table 4 Treatment modalities for 148 patients with primary carcinoma

	Parotid ($n = 117$)	Submandibular ($n = 8$)	Minor ($n = 23$)
Definitive surgery with or without radiotherapy			
Resection	67	4	14
Radical resection*	30	2	4
Total	97	6	18
Adjuvant radiotherapy	63	5	4
Neck dissection	7	0	0
Radical radiotherapy alone	20	2	5

*Radical parotidectomy (partial nerve sacrifice, eight patients; nerve trunk resection only, five, extended resection, 17). Radical submandibular surgery included muscles, nerves adjacent to the gland, and part of the floor of mouth. Radical resection of minor salivary glands included two hemimaxillectomies and two hemimandibulectomies

Patients referred from elsewhere with carcinoma were a heterogeneous group and treatment was determined by several factors: previous radiotherapy, extent of tumour, and nodal and distant metastases.

Statistical analysis

Survival curves were calculated with Kaplan–Meier life tables using cancer-related mortality as the endpoint. Patients who died from causes unrelated to cancer were censored at the time of death. Survival rates were not calculated for subgroups where the number of patients at risk, at a particular time, was less than five. The log rank test was used to determine the significance of variables against survival. Only patients treated with definitive intent were included. Multivariate analysis of prognostic factors was performed with the Cox proportional hazards regression model using the Statistical Package for Social Sciences (Superior Performing Software Systems, Chicago, Illinois, USA).

Results

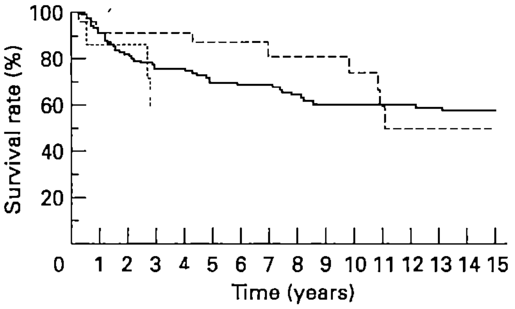
Benign tumours

Following the treatment of new parotid pleomorphic adenomas, there were nine recurrences (1·6 per cent) 1–21 years after operation (median follow-up 12·5 (range 1–34) years). There was no recurrence in the 19 patients who received radiation following surgical spillage. No recurrence was recorded in 21 submandibular gland excisions and only one following treatment of 22 new pleomorphic adenomas in the minor glands. The recurrence rate in patients treated with parotid pleomorphic adenomas referred following treatment elsewhere was 15 per cent (median follow-up 14 (range 1–39) years). Malignant degeneration of histologically proven pleomorphic adenomas was observed in four patients.

Malignant tumours

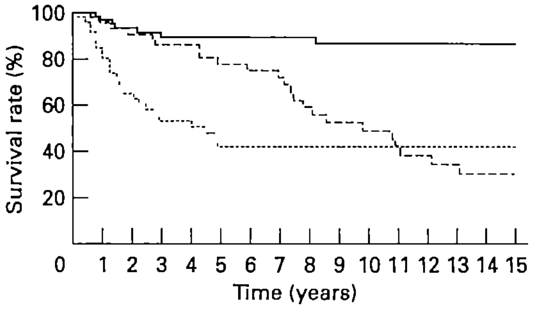
The disease-free survival rate for patients with primary carcinomas at all sites ($n = 148$) was 58, 47 and 45 per cent for 5, 10 and 15 years respectively, and for patients referred secondarily ($n = 61$) 51, 43 and 37 per cent at 5, 10 and 15 years respectively. Patients with recurrent disease had a worse outcome, but the difference was not significant (log rank $\chi^2 = 0·55$, 1 d.f., $P = 0·46$). In the 27 patients treated palliatively median survival was 6 (range 2–75) months.

Figs 2, 3 and *4* show the results of survival correlated to anatomical site, histology and clinical stage. In the



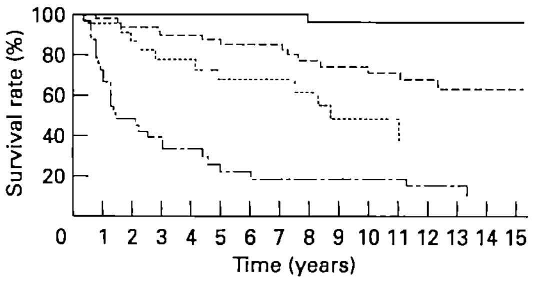
No. at risk				
Parotid	117	68	44	30
Submandibular	8	3*	2	2
Minor	23	18	10	5

Fig. 2 Determinate survival according to anatomical site. ———, Parotid gland; – – – –, submandibular gland; -------, minor salivary glands. *Five patients were at risk at 3 years, at which time the survival rate was 57 per cent. Log rank $\chi^2 = 0·35$, 2 d.f., $P = 0·84$



No. at risk				
Group 1	60	45	30	15
Group 2	42	29	14	8
Group 3	46	15	12	11

Fig. 3 Histological types were categorized into three groups for survival analysis (see main text). ———, Group 1; – – – –, group 2; ------, group 3. Log rank $\chi^2 = 25·91$, 2 d.f., $P < 0·0001$



No. at risk				
Stage I	36	29	21	17
Stage II	50	37	23	12
Stage III	24	13	5	2
Stage IV	33	6	5	2

Fig. 4 Determinate survival according to clinical stage (American Joint Committee on Cancer) ———, Stage I; – – – –, stage II, ------, stage III, – – · –, stage IV. Log rank $\chi^2 = 78·89$, 3 d.f., $P < 0·0001$

univariate analysis, tumour stage and histological type were significant predictors of outcome. Histological type, when judged by survival, fell into three prognostic groups: group 1 (good) – low-grade mucoepidermoid carcinoma, acinic cell carcinoma and adenocarcinoma; group 2 (intermediate) – adenoid cystic carcinoma; and group III (poor) – high-grade mucoepidermoid carcinoma, malignant mixed tumour, squamous cell carcinoma and undifferentiated carcinoma. Multivariate analysis with the Cox model demonstrated that clinical staging (relative risk = 6·4, $P < 0·001$, 95 per cent confidence interval (c.i.) 3·4–11·8) and, with less significance, group 3 tumours (relative risk = 2·2, $P = 0·004$, 95 per cent c.i. 1·3–3·8) were independent prognosticators.

Locoregional failure rates following treatment of primary carcinoma were: parotid, 37 per cent (43 of 117); submandibular, five of eight; minor glands, eight of 23. Distant failure occurred in 24 per cent (35 of 148) of newly treated malignancies despite curative intent. For all carcinomas, clinically detectable distant metastases were documented in 66 patients (pulmonary, 64 per cent; cerebral, 24 per cent; skeletal, 21 per cent; hepatic, 9 per cent). The true incidence was undoubtedly higher because relatively few who died were subjected to autopsy.

Complications

Major complications were few. Permanent postoperative facial injury (unexpected and expected) was less than 3 per cent (19 of 722) following treatment of primary benign parotid disease rising to 36 per cent (35 of 97) in malignant tumours. Four patients in the study developed osteoradionecrosis. There were two postoperative deaths, both early in the series and attributed to cardiopulmonary complications. An additional death was attributed to a late complication, namely meningitis secondary to chronic suppurative otitis media following surgery and radiation to the parotid area.

Discussion

Salivary gland tumours are uncommon and the understanding of their behaviour relies chiefly on publications of large clinical series from individual institutes[8–10].

The recurrence potential of pleomorphic adenomas is well recognized and the rate of 1·6 per cent for the parotid gland in this series is similar to that in other reports[9,11–13]. Some recurrences were seen many years after the initial treatment, emphasizing the need for long-term follow-up. Once a tumour had recurred, the patient had an increased risk of further disease (2 *versus* 15 per cent). Malignant degeneration was observed in four pleomorphic adenomas; in all, there had been repeated recurrences and intervention with the tumours present for at least 25 years. This relationship has been noted by other authors[11,14].

The clinical diagnosis of malignancy is obvious when advanced, but over 50 per cent of the carcinomas in this series presented as discrete lumps and were clinically indistinguishable before operation from benign conditions. Clinical assessment was supported by computed tomography in the latter part of the series but fine-needle aspiration cytology (FNAC) was not used because the technique was not well established for most of the study period. While the accuracy of FNAC has improved in the past decade[15], its importance in clinical management decisions remains controversial[16]. Frozen sectioning was used early in the series, but as in other studies[17] errors were encountered and the technique was abandoned.

Anatomical site was not a significant prognostic factor. Submandibular gland malignancy is generally considered to have a worse prognosis than parotid cancer but recent reports have shown that survival can be improved by comprehensive local excision in conjunction with regional dissection as primary treatment[18,19]. Minor gland malignancy, other than that arising within the oral cavity, is associated with poor survival[10] but was not included in this series.

The grouping of tumours into three categories (good, intermediate and poor) was based on clinical behaviour and not histological grading. The latter is controversial and variations exist between institutions. With the exception of mucoepidermoid carcinomas, grading was not performed routinely at the Christie Hospital and, therefore, survival was not correlated to this factor. Histological type influenced survival and supports a model of different 'degrees' of malignancy[20]. Malignant mixed tumour, undifferentiated and squamous cell carcinomas have the worst prognosis, whereas mucoepidermoid and acinic cell carcinomas have the best. On the other hand, data on the survival of adenocarcinomas vary considerably: Matsuba *et al.*[21] reviewed eight large studies and reported a cumulative survival rate at 5 years of between 16 and 85 per cent. This tumour category is a heterogeneous group of histological subtypes[5] and this is a possible explanation for the differences noted. Adenoid cystic carcinoma is a protracted disease characterized by late recurrences and metastases and consequently requires long-term follow-up to assess prognosis.

This study has confirmed clinical stage as an independent predictor of survival[10,20]. Interestingly, survival was not affected in patients with malignant tumours referred secondarily. A probable explanation is referral bias: patients with recurrent carcinoma considered curable were referred for secondary treatment, whereas those with no prospect of cure were not.

Throughout this series, the surgical philosophy was remarkably consistent. Radiotherapy was used as an adjuvant to surgery for malignant disease and selectively for benign disease, despite previous claims that salivary gland tumours are radioresistant[22]. With respect to carcinomas, this approach was commenced in the 1950s and is vindicated by contemporary studies with comparative data, which report better locoregional control (and possibly improved survival) with combined therapy for high stage[23] and high grade[24] cancers compared with resection alone.

Acknowledgements

The authors thank Messrs O. A. Shaheen, J. D Maynard and R. G. Williams for critical appraisal of the manuscript.

Tribute

The authors wish this paper to stand as a tribute to the outstanding surgery of the late Alan Nicholson who commenced this work in 1947 and who died on 22 June 1992. He kept the most meticulous records and followed his patients assiduously, long into his retirement. His perfectionism and desire to follow his patients ever longer prevented him from committing this

work to publication Without his diligence and the loyalty of his patients, who returned year after year, this series could never have been brought to a meaningful conclusion.

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British Journal of Surgery 1996, 83, 1755–1757

Cyclosporin A and multiple fibroadenomas of the breast

A. D. BAILDAM, R. M. HIGGINS*, E. HURLEY†, A. FURLONG, J. WALLS, M. C. VENNING*, P. ACKRILL* and R. E. MANSEL

*Departments of Surgery, †Radiology and *Renal Medicine, University Hospital of South Manchester, Manchester, UK*

Correspondence to. Professor R. E Mansel, University Department of Surgery, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

Multiple bilateral fibroadenomas are uncommon. This finding in four women who had received renal transplants prompted further inquiry. A prospective study was performed on 39 women under the age of 55 years who had received a renal transplant at least 1 year earlier. Clinical examination and breast ultrasonography were performed. Factors considered included immunosuppressive therapy, concurrent medication and renal function. Blood was taken for estimation of oestradiol, prolactin, follicle-stimulating hormone (FSH) and sex hormone binding globulin levels. Fibroadenomas were found in 13 of 29 women who had received cyclosporin A: multiple in ten and bilateral in five. No abnormal breast findings were seen in 10 patients immunosuppressed with steroids and azathioprine alone ($\chi^2 = 7\cdot30$, 1 d.f., $P < 0\cdot01$). Serum oestradiol concentration was raised in women with fibroadenomas compared with that in those with normal breasts ($P < 0\cdot05$) and the level of FSH was lower ($P < 0\cdot01$). Cyclosporin A may act on breast fibroblasts by humoral mechanisms and direct action.

Solitary fibroadenoma of the breast is a common diagnosis in young women, and presents as a well circumscribed mass in an otherwise normal breast[1–3]. Multiple fibroadenomas in one individual and bilateral multiple fibroadenomas are extremely uncommon; no current data exist on the incidence or natural history[4]. Familial factors and oral contraceptive pill use have been described as aetiological factors in the pathogenesis of bilateral multiple fibroadenomas[5,6]. The present study was initiated after four young women, all recipients of renal transplants, presented with symptoms of bilateral multiple breast lumps, and excision biopsy confirmed the diagnosis of fibroadenomas. A protocol was, therefore, established to investigate the prevalence of fibroadenomas in a cohort of premenopausal women who had undergone renal transplantation.

Patients and methods

A group of women from the renal clinic of the University Hospital of South Manchester who had undergone renal transplantation at least 1 year before the study and who were aged less than 55 years were studied. Patients were invited to take part by letter. At the next routine renal clinic visit they were interviewed and underwent breast examination and ultrasonography of both breasts. The radiologist and clinician had no knowledge of immunosuppressive treatment or any other clinical variables.

Particular attention was paid to the renal history, drug therapy and immunosuppressive agents, menstrual and reproductive history, oral contraception, smoking and alcohol. Blood was withdrawn for haematological and biochemical factors and hormone profiles. Menstrual cycle status was recorded. Dose and duration of cyclosporin A, azathioprine and prednisolone were recorded and plasma concentrations of cyclosporin A were measured. Statistical analysis was performed with the χ^2 test, Mann–Whitney U test and unpaired t test.

Paper accepted 21 February 1996

Results

Thirty-nine women with renal transplants were examined; none was of Afro-Caribbean origin, in whom multiple fibroadenomas are more common. Some 29 women were either currently taking cyclosporin A ($n = 28$) or had done so 6 months or more previously ($n = 1$). Thirteen women were found to have fibroadenomas; these were multiple in ten and bilateral in five. Four patients had five or more fibroadenomas. Eleven patients were previously unaware of any breast abnormality. Fibroadenomas were found in 11 patients by clinical examination and ultrasonography, and in two by ultrasonography alone.

A comparison of patient and treatment variables between those with fibroadenomas and those without is shown in *Table 1*. Serum follicle-stimulating hormone (FSH) concentration was significantly lower in patients with fibroadenomas ($P < 0\cdot01$) compared with that in those with normal breasts, and oestradiol concentrations were higher ($P < 0\cdot05$).

The menstrual cycle status of those with fibroadenomas was not significantly different from that in those with normal breasts (*Table 2*).

There was no association between the presence of fibroadenomas and azathioprine or steroid use but there

Table 1 Patient profiles, serum follicle-stimulating hormone, oestradiol and prolactin concentrations

	Fibroadenomas	Normal breasts	P*
Age (years)	35·1(6·7) (27–50)	39·6(9·6) (20–53)	
Time after transplant (months)	57·8(33·4) (23–126)	81·0(50·2) (14–187)	
Follicle-stimulating hormone (munits/l)	4·7(2·3)	22·2(21·9)	<0·01
Prolactin (munits/l)	398(208)	276(175)	n.s.
Oestradiol (pmol/l)	569(162)	283(61)	<0·05

Values are mean(s.d.) (range) n.s., Not significant. *Mann–Whitney U test

Table 2 Menstrual cycle status

	Fibroadenomas ($n = 13$)	Normal breasts ($n = 26$)
Follicular phase	10	17
Luteal phase	2	4
Amenorrhoea	1	5

was a highly significant positive correlation with the use of cyclosporin A. Of 29 patients currently receiving cyclosporin A or who had previously done so, 13 had fibroadenomas, whereas no patient had fibroadenomas from the group that was receiving steroids or azathioprine ($\chi^2 = 7{\cdot}30$, 1 d.f., $P < 0{\cdot}01$). No differences were found in cyclosporin A dosage, blood concentration or length of treatment time between those on cyclosporin A who had fibroadenomas and those who did not. There was no association between the occurrence of multiple fibroadenomas and the other medications considered.

No patient was currently taking the oral contraceptive pill, although a number had done so in the past.

Cyclosporin A is known to cause gingival hypertrophy and this effect is thought to be mediated by the gingival fibroblast[7]. There was no association between the presence of fibroadenomas and gingival hypertrophy.

Discussion

There was a positive association between the use of cyclosporin A for immunosuppression after renal transplantation and the prevalence of multiple fibroadenomas of the breast.

Two patients with benign breast lumps on cyclosporin A have been reported previously[8]. In one patient the masses resolved after withdrawal of cyclosporin A. This did not occur in one patient in the present study who at the time of examination was on steroids but who had previously taken cyclosporin A.

Cyclosporin A has well recognized side-effects, the causative mechanisms of which are poorly understood[7,9]. Gingival hypertrophy is widely encountered and patients frequently require oral surgery for its correction[10]. In this situation cyclosporin is thought to act by a direct effect on gingival fibroblasts, promoting both proliferation and collagen production[11,12]. There was no association between the presence of gingival hypertrophy and the presence of fibroadenomas. This might imply that the mode of action of cyclosporin A in the promotion of breast fibroadenoma is different from its action on the gingiva. Its biological activity has been described[13–18].

Some populations of lymphocytes and fibroblasts exhibit cyclosporin receptors[19]. Cyclosporin A could potentially promote fibroadenomas, therefore, by a direct action on fibroblasts. Cyclosporin A has also been found to block prolactin receptors in T lymphocytes[20,21].

Those with fibroadenomas had higher serum oestradiol concentrations, with lowering of FSH. Cyclosporin A has an effect on the hypothalamopituitary axis in rats: serum luteinizing hormone secretion is inhibited and testicular testosterone biosynthesis decreased, and this feature is dose-dependent[22]. Gynaecomastia may occur in male patients; this has been attributed to an alteration in the androgen to oestrogen ratio[23,24]. Endocrine mechanisms may have a role in this clinical situation. Perturbation of endocrine function may be as much due to relief of uraemia after transplantation as to cyclosporin A[25].

Further study of the mechanism of fibroadenoma promotion by cyclosporin A is needed to gain more insight into the stimulation of growth of breast tumours. The effect may be mediated by a hormonal action and as a direct effect on the breast fibroblast.

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Case report

Thoracoscopic parathyroidectomy of an ectopic mediastinal adenoma

P. GULLSTRAND, G. OLSSON,
M. OLSSON, K. SUNDKVIST,
B. LEIDNER* and O. MÅRTENSSON*
*Departments of Surgery and *Radiology, Hospital of Oskarshamn, Box 701, S-572 28 Oskarshamn, Sweden*
Correspondence to: Mr P. Gullstrand

Thoracoscopic parathyroidectomy in a patient with an adenoma in the lower mediastinum is described. This is a new method, probably reducing morbidity compared with median sternotomy, and has to the authors' knowledge not been described before.

Case report

A 67-year-old woman with hypertension and renal calculi was investigated for tiredness and polydipsia. She had hypercalcaemia (serum calcium level 3·6 mmol/l, ionized calcium level 2·01 mmol/l), a parathyroid hormone level of 512 ng/l, serum creatinine concentration 158 μmol/l and alkaline phosphatase level 6·3 μkat/l. Ultrasonographic examination of the neck was normal. Contrast-enhanced computed tomography (CT) of the thorax showed a possible ectopic parathyroid adenoma (*Fig. 1*).

Paper accepted 17 February 1996

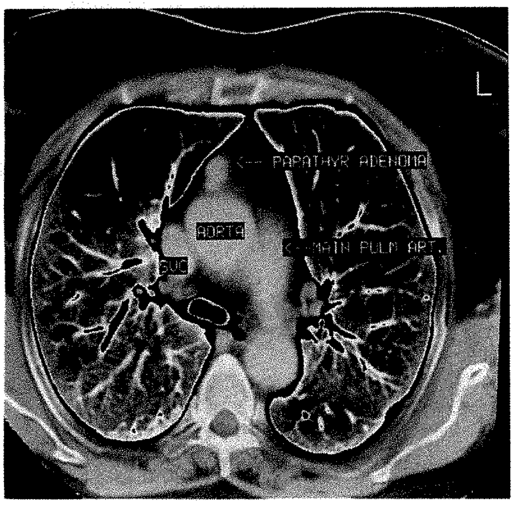

Fig. 1 Contrast-enhanced computed tomogram of the thorax revealing an intensively enhancing 10 × 18 mm solid structure embedded in the mediastinal fat anterior to the ascending aorta. The finding is consistent with an ectopic parathyroid adenoma. SVC, superior vena cava

At operation, the patient was positioned with the right side 30° upwards. The Veress needle was inserted in the anterior axillary line between the third and fourth ribs and insufflated to a maximum pressure of 6 mmHg. At this site a 12-mm trocar (Johnson and Johnson/Ethicon Endo-Surgery, Sollentuna, Sweden) was inserted for the 10-mm (0°) endoscope (Olympus Optical, Solna, Sweden). A further 12-mm trocar was inserted just below the first and finally a 5-mm trocar was inserted lateral to the mid-clavicular line between the second and third ribs. The adenoma was identified in the anterior mediastinum, above and medial to the right atrium and ventral to the aortic arch. The pleura was opened and the adenoma was resected after its stalk had been clipped. It was removed through the lower 12-mm port, after widening it to 18 mm, and was sent for peroperative frozen sectioning, which showed parathyroid tissue without clear differentiation between hyperplasia and adenoma. Finally, an 18-Ch chest drain was inserted through the lower port. The drain was removed on the first postoperative day, the serum calcium level was normal on the second, and on the third day the patient was discharged, feeling well.

Discussion

Due to their embryonic origin the lower parathyroids have a wide variety of locations[1]. In primary hyperparathyroidism 15–20 per cent of adenomas are ectopic, sometimes in the lower mediastinum[1]. In this patient the right lower parathyroid was detected in the chest at CT imaging. Thoracoscopic exploration of the mediastinum was performed, saving a neck exploration until later, if needed. If thought necessary, a methionine positron emission tomographic scan, a Sestamibi scan or an angiogram could have been used to confirm the location of the ectopic parathyroid. Alternatively angiographic ablation of mediastinal adenomas has been described[2]. The technique is difficult and does not retrieve tissue for histopathological examination. The thoracoscopic approach may reduce morbidity, gives tissue for histopathological diagnosis and shortens hospital stay compared with conventional sternotomy.

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British Journal of Surgery 1996, **83**, 1758–1762

A 45-year perspective of congenital diaphragmatic hernia

K. VANAMO

Children's Hospital, University of Helsinki, Helsinki, Finland
Correspondence to: Dr K. Vanamo, Department of Paediatric Surgery, Kuopio University Hospital, 70 211 Kuopio, Finland

The records of 174 consecutive patients with congenital diaphragmatic hernia were reviewed to analyse the changes in the presentation, treatment and outcome during the 45-year interval from 1948 to 1992. For comparison the period was divided into years 1948–1962, 1963–1972, 1973–1982 and years 1983–1992. The proportion of high-risk cases (symptomatic within 6 h of birth) increased from 50 per cent during the first period to 77 per cent during the second, to 86 per cent during the third and to 94 per cent during the fourth. The primary mortality rate (death within 30 days of diaphragmatic repair) increased from 25 per cent during the first period to 35 per cent during the second, 46 per cent during the third and 49 per cent during the fourth. No change occurred in the proportion of infants with diaphragmatic hernia who were stillborn or who died in the maternity unit. Post-mortem lung weight was available in 56 children. Severe pulmonary hypoplasia correlated with early postoperative death and clinical severity. The mean(s.d.) lung weight ratio (combined lung weight divided by the lung weight expected for the body-weight) decreased from 0·70(0·49) during the second period to 0·56(0·36) during the third and 0·40(0·18) during the fourth. The increased proportion of more severe cases with very hypoplastic lungs explains the rise in the mortality rate of patients operated on for congenital diaphragmatic hernia. This may reflect a real change in the disease spectrum rather than improved referral.

The mortality rate in patients with congenital diaphragmatic hernia remains high despite advances in prenatal diagnosis, maternal transport, delivery room resuscitation, timing of the repair and modern intensive care management[1,2]. This is usually attributed to the manifestation of 'hidden mortality' – the inclusion of infants who previously died unrecognized[3–5]. On the other hand, conflicting reports have been published on the changing severity of the condition. Some found an increase in the proportion of patients who arrived intubated, at an early age, with large diaphragmatic defects, who required postoperative ventilatory assistance and had hypoplastic lungs at autopsy[1,6]. Others concluded that quicker referral rather than transfer of more severely affected children accounts for the apparent increase of disease severity[7]. This study documents the experience in the treatment of congenital diaphragmatic hernia in a single tertiary care children's hospital over a period of 45 years.

Patients and methods

A total of 174 infants with Bochdalek-type congenital diaphragmatic hernia had operations during the 45-year interval from 1948 to 1992 in the Children's Hospital, University of Helsinki. The hospital records and autopsy reports were reviewed for analysis.

One hundred patients (57 per cent) were male and 74 (43 per cent) were female. Mean maternal age and parity did not differ significantly from those of all Finnish newborns during the study. Mean(s.d.) duration of pregnancy was 38·7(2·6) (range 29–43) weeks. Some 24 per cent of the newborns were younger than 36 weeks of gestational age. The mean(s.d.) birth-weight was 3128(600) (range 800–4750) g and 13 per cent weighed less than 2500 g.

Ten patients (6 per cent) had a family history of congenital anomaly, including two with a family history of congenital diaphragmatic hernia and five with cardiac anomalies. Thirteen patients (7 per cent) had a family history of other abnormalities, including hypogammaglobulinaemia, haemophilia, mental retardation, prematurity and unexplained neonatal death.

A complication occurred during 82 pregnancies (47 per cent). Mild pre-eclampsia and premature labour were the most common problems (58 cases, 33 per cent). Polyhydramnios was recorded in 32 cases (18 per cent). A prenatal diagnosis of diaphragmatic hernia was made in eight patients at the median gestational age of 33 (range 13–36) weeks.

Seventy associated abnormalities were reported in 58 patients (33 per cent). Some 23 (13 per cent) had major anomalies: 15 cardiac anomalies, four intestinal atresias and one case each of biliary atresia, renal agenesis, Noonan's syndrome and Kartagener's syndrome. Cryptorchidism was the commonest minor anomaly (16 cases, 16 per cent of males). No chromosomal anomalies were detected among the 11 patients screened.

All eight patients with a prenatal diagnosis of diaphragmatic hernia underwent immediate resuscitation after birth. In all, 126 patients (72 per cent) became symptomatic within 6 h postnatally; respiratory distress was the main symptom in 123 (98 per cent). One or more of the classical clinical signs of cardiac displacement, silent breathing sounds, scaphoid abdomen or thoracic deformity were present in 72 cases (57 per cent). Thirty-three patients (19 per cent) presented more than 6 h postnatally. Respiratory distress was the main symptom in 13 of those who presented late; the rest developed respiratory infection, vomiting or failure to thrive. Six asymptomatic cases were diagnosed incidentally. In one case the exact onset of symptoms was not recorded.

The operative principles were conventional until 1990. All symptomatic infants had surgery at the earliest suitable moment. Since 1990 a policy of preoperative stabilization and delayed primary operation had been adopted[8,9]. Extracorporeal membrane oxygenation (ECMO) was utilized only once in this series.

Surgical details

A transverse abdominal incision was used in 134 patients (77 per cent) and a longitudinal (paramedian) incision in 16 (9 per cent). An unspecified laparotomy was performed in ten patients. A thoracotomy was done in eight cases (5 per cent) and a thoracolaparotomy in four (2 per cent). Details of the incision were missing in two patients. Some 153 hernias (88 per cent) were left sided and 21 (12 per cent) were right sided. Two patients had a concurrent eventration of the contralateral

Paper accepted 10 March 1996

diaphragm. The defect was posterolateral in 152 patients (87 per cent). On the left side the rest of the defects were anterolateral or posteromedial. Four right-sided hernias consisted of a local bulge of the liver.

The size of the diaphragmatic defect was recorded in 119 cases. It was described as large in 53 (45 per cent), moderate in 50 (42 per cent) and small in 16 (13 per cent). Five patients had a complete agenesis of the hemidiaphragm. A thin avascular hernial sac was present in 15 cases (9 per cent), more often on the right side ($P < 0{\cdot}05$). The size of the ipsilateral lung was described in 103 cases. It was normal in six (6 per cent), smaller than normal in 41 (40 per cent) and very small in 56 (54 per cent). The amount and type of herniated organs were recorded in 166 patients. The liver was present in the hernia in 62 cases (37 per cent).

The diaphragm was repaired with sutures in 132 cases (76 per cent). When the defect was too large for direct suture a local flap comprising muscle, fascia, peritoneum or pericardium (12 patients, 7 per cent) or prosthetic material (27, 16 per cent) was utilized depending on the surgeon's choice. Both techniques were used progressively more often during later years.

Primary closure of the incision was possible in 140 patients (80 per cent). In 33 patients (19 per cent) a controlled abdominal hernia was created by closing the skin only. This was usually repaired 10–14 days later.

An ipsilateral pleural drain was inserted in 99 (57 per cent) patients; 46 (26 per cent) received bilateral drains and one patient received only a contralateral drain. Mean(s.d.) duration of pleural drainage was 4·0(3·6) (range 0–15) days. Median hospital stay in survivors was 21 (mean 31, range 8–217) days.

Perioperative management

For analysis, the study period was divided into four according to the evolution of perioperative management: 1948–1962, 1963–1972, 1973–1982 and 1983–1992. There were 32 patients in the first group, 49 in the second, 54 in the third and 39 in the fourth.

Postoperative ventilation was not used during the first period. Routine postoperative ventilation and invasive monitoring emerged during the second period. During the third period intermittent mandatory ventilation, positive end-expiratory pressure, prolonged postoperative muscle relaxation and pulmonary vasodilators became available. The modern life-supporting techniques of high-frequency ventilation and ECMO emerged during the last period.

Statistical analysis

Statistical significance was assessed with the *t* test and analysis of variance (ANOVA) for normally distributed continuous data. The Mann–Whitney *U* test was used with non-normal data. Categorical variables were assessed with the χ^2 test. Linear regression analysis was used to determine correlation between two continuous variables. Significance level was set at $P < 0{\cdot}05$.

Results

The following clinical criteria, recorded throughout the whole study, were used to assess the severity of the condition: birth-weight, presence of major associated anomalies, respiratory distress at presentation, age at the onset of symptoms and presence of liver in the hernia (*Table 1*). According to the above criteria, the proportion of more severe cases increased over time (*Table 2, Fig. 1*). No significant difference was found between survivors and non-survivors in terms of maternal age or parity, sex or gestational age of the patient, presence of other major anomalies, symptoms other than respiratory distress, recorded classical clinical signs, the presence of a hernial sac, the side of the diaphragmatic defect, postoperative pleural drainage or the use of pleural suction.

Some 157 complications were recorded in 109 patients (63 per cent). Pneumothorax was the most common complication (ipsilateral 24, contralateral 19, bilateral 15, unspecified one) followed by megaoesophagus or gastro-

Table 1 Comparison of simple clinical criteria in survivors and non-survivors of congenital diaphragmatic hernia

	Survivors	Non-survivors	*P*
Mean birth-weight (g)	3239	2951	0·002*
Major anomalies (%)	8	22	0·015†
Respiratory distress (%)	77	94	0·005†
Symptoms within 6 h of birth (%)	68	95	0·0002†
Liver in the hernia (%)	21	63	0·0001†

**t* test; †χ^2 test

Table 2 Comparison of treatment periods in 174 patients with congenital diaphragmatic hernia

	1948–1962	1963–1972	1973–1982	1983–1992	*P*
Mean birth-weight (g)	3160	3201	3137	2980	n.s.*
Major anomalies (%)	3	18	15	13	n.s.†
Respiratory distress (%)	66	82	87	97	0·004†
Symptoms within 6 h of birth (%)	50	77	86	94	0·0001†
Liver in the hernia (%)	10	38	48	44	0·005†

*Analysis of variance; †χ^2 test

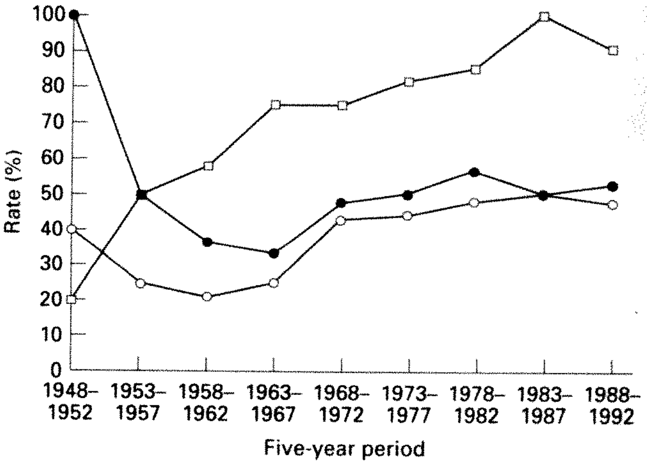

Fig. 1 Overall primary mortality (○, death within 30 days of diaphragmatic repair), primary mortality of high-risk cases (●, symptomatic within 6 h of birth) and percentage of high-risk cases (□) during 5-year periods in 1948–1992

oesophageal reflux (ten patients), pulmonary atelectasis (nine), renal insufficiency (nine) and wound infection (eight). The incidence of pneumothorax, especially bilateral pneumothorax, increased significantly during the last three periods ($P<0{\cdot}05$) (*Fig. 2*). The incidence of all postoperative complications also increased, but the difference was not statistically significant (*Fig. 2*). Fourteen patients (8 per cent) had chronic sequelae such as bronchopulmonary dysplasia, chronic respiratory insufficiency, pulmonary hypertension, total parenteral nutrition-associated cholestasis, subdural effusion or epilepsy. The incidence of chronic sequelae increased during the study period, but the difference was not statistically significant (*Fig. 2*).

Primary mortality was defined as death within 30 days of diaphragmatic repair. The overall primary mortality rate was 40 per cent (69 patients). It increased continuously from 25 per cent during the first period to 35 per cent during the second, 46 per cent during the third and 49 per cent during the fourth (*Table 2*, *Fig. 3*). Ninety-four per cent of those who died (65 of 69 patients) were high-risk cases. All eight prenatally diagnosed patients died, seven of them within 14 h of birth.

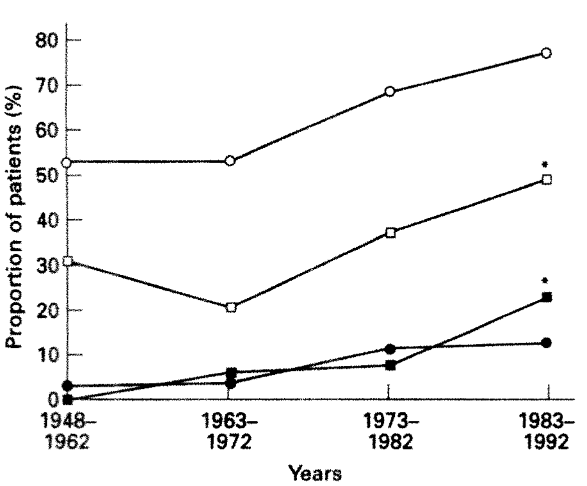

Fig. 2 Proportion of patients with postoperative complications and chronic sequelae during different periods from 1948 to 1992: ○, all complications; □, all pneumothoraces, ■, bilateral pneumothoraces; ●, chronic sequelae. $^*P<0{\cdot}05$ (all groups, χ^2 test)

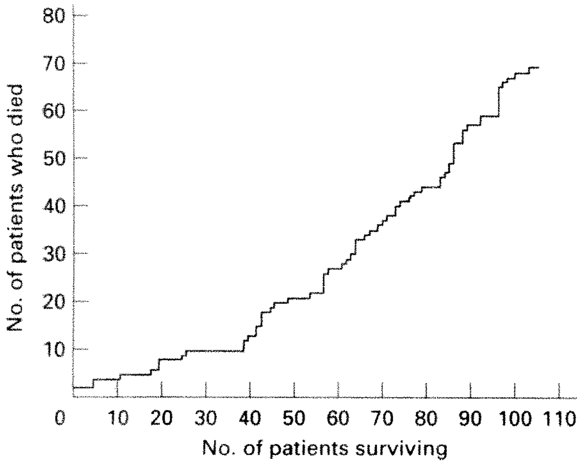

Fig. 3 Primary mortality in congenital diaphragmatic hernia. Consecutive plot of the outcome in 174 patients in the period 1948–1992. The slope of the curve represents the mortality rate

Autopsy findings

Lung weight. Lung weight was available in 56 of the 69 children who died, and was expressed as the lung weight ratio (LWR): combined lung weight divided by the lung weight expected for the body-weight. Expected lung weight was estimated according to Sung and Singer[10]. Ninety per cent had an LWR equal to or less than 0·51. Low LWR correlated with early diagnosis ($r=0{\cdot}60$, $P=0{\cdot}0001$), early death ($r=0{\cdot}70$, $P=0{\cdot}0001$) and an intrathoracic liver ($P=0{\cdot}03$, Mann–Whitney U test). Mean(s.d.) LWR of those who died within 48 h of operation was 0·40(0·12) (range 0·19–0·76).

A best pH less than 7, arterial partial pressure of carbon dioxide greater than 8·0 kPa (60 torr) and of oxygen of less than 6·7 kPa (50 torr) are usually considered to indicate an unfavourable prognosis[11]. There was a significant difference in both the outcome and mean LWR between the different prognostic groups based on blood gas criteria (*Table 3*). The mean(s.d.) LWR of those who died showed a steady decline over time: 0·70(0·49) for the second period, 0·56(0·36) for the third and 0·40(0·18) for the fourth ($P<0{\cdot}05$, the fourth *versus* second period, ANOVA).

The weight of the contralateral lung, while always greater, was directly proportional to the weight of the ipsilateral lung ($r=0{\cdot}67$, $P=0{\cdot}0001$).

Kidney weight. Kidney weight was expressed as the kidney weight ratio (KWR): combined kidney weights divided by the kidney weight expected for the body-weight. Expected kidney weight was estimated using data by Sung and Singer[10]. Mean(s.d.) KWR was 1·01(0·29) (range 0·61–1·85). There was no correlation between KWR and LWR when patients with renal agenesis, pneumonia, sepsis and major cardiac anomalies were excluded and a positive correlation ($r=0{\cdot}62$, $P=0{\cdot}0001$) when all patients were included.

Table 3 Number of patients with congenital diaphragmatic hernia, outcome and mean lung weight ratio in different porgnostic groups based on preoperative blood gas criteria

Prognostic group	No. of patients*	No. who died	Mean (range) LWR at autopsy
Unfavourable prognosis ($P_{aO_2}<6{\cdot}7$ kPa and ($P_{aCO_2}>8{\cdot}0$ kPa and pH < 7)	9	9	0·34 (0·23–0·56)
Intermediate prognosis ($P_{aO_2}>6.7$ kPa or ($P_{aCO_2}<8{\cdot}0$ kPa or pH > 7)	21	13	0·46 (0·30–0·84)
Favourable prognosis ($P_{aO_2}>6{\cdot}7$ kPa and ($P_{aCO_2}<8{\cdot}0$ kPa and pH > 7)	26	6†	0·62 (0·30–1·32)‡

*Only patients with complete data are included. LWR, lung weight ratio (combined lung weight divided by lung weight expected for the body-weight). †$P=0{\cdot}0001$ (all groups, χ^2 test); ‡$P<0{\cdot}05$ (favourable *versus* unfavourable prognosis, analysis of variance)

'Hidden' cases. Since 1961 a post-mortem examination was performed routinely in all infants who were stillborn or died in the maternity unit. There were 29 such cases with a diaphragmatic hernia within the period from 1961 to 1992. These cases are not included in the mortality figures. Five pregnancies were terminated electively, five infants were stillborn and the rest died shortly after birth in spite of resuscitation. Nineteen of the 29 infants had associated anomalies. Seven had central nervous system, ten had cardiac and three had chromosomal anomalies. Mean(s.d.) LWR was 0·29(0·13) (range 0·12–0·62). The relative proportion of those who were stillborn or who died before referral (the hidden mortality) stayed relatively constant in the hospital's maternity unit (*Fig. 4*), whereas the mortality rate of infants with congenital diaphragmatic hernia referred from that unit increased throughout the same period (*Fig. 5*).

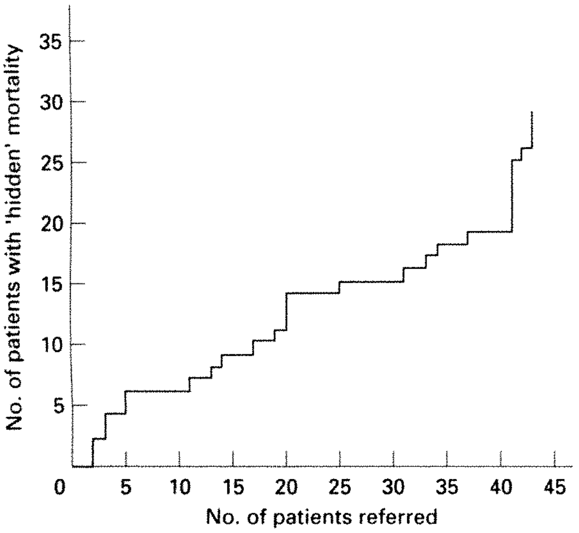

Fig. 4 'Hidden mortality' of congenital diaphragmatic hernia in a single maternity unit during 1961–1992. Consecutive plot of infants who were either stillborn, aborted or who died in the maternity unit *versus* those referred from that unit. The slope of the curve represents the proportion of the 'hidden' cases

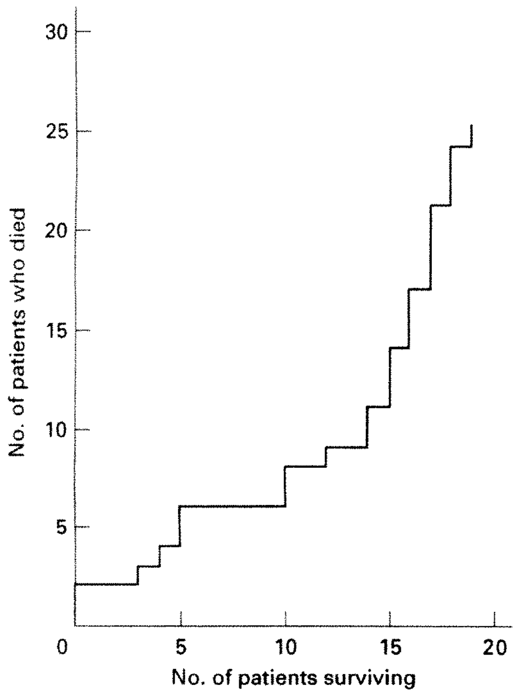

Fig. 5 Primary mortality of patients with congenital diaphragmatic hernia referred from a single maternity unit during 1961–1992. Consecutive plot of the outcome; the slope of the curve represents the mortality rate

Discussion

During the 45 years under study the mortality rate from congenital diaphragmatic hernia increased despite the remarkable changes that took place in the perioperative management.

Mortality was associated with low birth-weight, presence of other major anomalies, respiratory distress, early onset of symptoms and an intrathoracic liver. A prenatal diagnosis was an ominous sign in this series as all eight patients wtih a prenatally detected congenital diaphragmatic hernia died, irrespective of the gestational age at diagnosis.

The proportion of infants with severe and early symptoms increased over the study period (*Fig. 1*, *Table 2*). Their survival did not improve during the past 30 years. These facts together account for the increase in the overall mortality rate. The chief cause of postnatal mortality in congenital diaphragmatic hernia is pulmonary hypoplasia[1,12]. As the lung weight of children who died cannot be compared with that of survivors, indirect evidence is needed[7,13]. These data show a significant positive correlation between the LWR and postoperative survival time. Ninety per cent of those who died within the first 48 h had a combined lung weight equal to or less than half of that expected. Low LWR also correlated with clinical severity, as indicated by early diagnosis and an intrathoracic liver.

All patients fulfilling the usual unfavourable blood gas criteria[11] died. Their mean LWR was 0·34. In an infant who weighed 3000 g this would indicate a combined lung weight[10] of 18 g. This is in accordance with Simson and Eckstein[7], who estimated critical lung weight to be 20 g. However, some patients with temporarily favourable blood gas values had lungs smaller than this. Either the prognostic blood gas criteria do not reflect the pulmonary hypoplasia accurately or some other factors influence the outcome. In either case, it would be beneficial to be able to estimate the degree of pulmonary hypoplasia directly and independently of ventilatory requirements. Several methods have been proposed[9,14–19], but a reliable, accepted, quantitative measure is still missing. Without this, it is difficult to assess the importance of factors such as pulmonary hypertension and surfactant deficiency or to compare series and treatments.

Feedback modulation of pulmonary growth by a growth factor derived from the kidneys has been proposed. Pulmonary hypoplasia associated with congenital diaphragmatic hernia would maximally stimulate this feedback loop resulting in continual stimulation of the kidneys and renal enlargement[20]. There was no evidence of renal enlargement or of an inverse relationship between kidney and lung weight in the present autopsy data.

The existence of 'hidden' mortality has been well documented[3,5]. In a recent prospective study 34 per cent of fetuses with a prenatal diagnosis of diaphragmatic hernia died *in utero*, or soon after birth[3]. However, the mere existence of hidden mortality does not explain the apparent increase in disease severity over time; a concomitant decrease in the hidden mortality rate is needed. During the interval for which data were available, no change in the hidden mortality rate in the hospital's maternity unit could be detected (*Fig. 4*), although the mortality rate of patients with congenital diaphragmatic hernia referred from that unit rose steeply during the same period (*Fig. 5*). Thus the alternative explanation, a genuine change in disease severity, cannot be ruled out.

The incidence of complications increased over time. Chronic sequelae and systemic complications attributable to prolonged intensive treatment were also more common during the last two periods. This, together with the increased incidence of associated anomalies during later periods, may significantly affect the long-term outcome of patients with congenital diaphragmatic hernia in future.

The survival rate for congenital diaphragmatic hernia in most centres is 50–60 per cent. A further 15 per cent of infants may survive if ECMO is available[21]. For the most severely affected babies prenatal intervention to correct the pulmonary hypoplasia may offer hope in the future.

Acknowledgements

This study was supported by the Foundation for Paediatric Research, Helsinki, Finland.

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Prospective randomized study of sulindac *versus* calcium and calciferol for upper gastrointestinal polyps in familial adenomatous polyposis

F. SEOW-CHOEN, V. VIJAYAN and V. KENG

Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 0315
Correspondence to: Dr F. Seow-Choen

Eighteen patients with familial adenomatous polyposis (FAP) who had previously undergone colectomy but had upper gastrointestinal polyps were studied in a double-blind randomized crossover trial comparing sulindac with calcium and calciferol. Sulindac produced a reduction in the crypt proliferation index in the gastric epithelium of patients but did not significantly affect duodenal mucosa. Calcium with calciferol did not have any effects on crypt proliferation index in patients with FAP.

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized by the formation of hundreds of colorectal adenomas and eventually colorectal cancer. As well as colorectal polyps and cancer, polyps may also be found in the stomach and duodenum of patients with FAP[1,2]. Cancer arising from these polyps is the leading cause of death in patients who have undergone large bowel resection[3].

Calcium has been shown to reduce colorectal epithelial proliferation and turnover and to protect against the development of neoplasia, although no clear effect on the number of rectal polyps has yet been shown[4–6]. Vitamin D also reduces epithelial cell proliferation and promotes cellular differentiation[4,7,8]. Oral administration of 150–400 mg per day of the non-steroidal anti-inflammatory drug (NSAID) sulindac also produces regression of colorectal adenomas after 6–16 weeks of treatment[9–13]. However, gastric and duodenal adenomas do not seem to be similarly affected[9,14]. One study[10] revealed that the greatest reduction in the number and size of colorectal polyps occurred before 6 months rather than 9 months of treatment, perhaps because of decreasing patient compliance or the development of drug resistance[10].

There is a clear link between the intensity of cellular proliferation and susceptibility to neoplasia[15]. In the large intestine, surgical or dietary manipulation that reduces cell growth or causes mucosal hypoplasia has a protective effect against experimental colorectal carcinogenesis. The cytokinetic status of the colorectal epithelium could therefore reflect the subject's susceptibility to colorectal neoplasia[16,17]. Indeed, an expansion in the proliferative zone of colonic crypts has been demonstrated in patients with FAP[4]. The effect of these medications on upper gastrointestinal neoplasia, however, has seldom been studied[18]. The effects of oral administration of sulindac and calcium carbonate with calciferol on upper gastrointestinal polyps and on the epithelium of the upper gastrointestinal tract in patients with FAP were examined.

Patients and methods

Eighteen patients with FAP and upper gastrointestinal polyps were studied. They had undergone either total colectomy and ileorectal anastomosis or total proctocolectomy and ileoanal anastomosis. All patients gave informed consent. Patients with a known adverse reaction to any drug used were excluded from the study.

A double-blind randomized crossover trial comparing sulindac with calcium and calciferol was carried out. Randomization was performed by allocation of random numbers. Patients allocated to the calcium and calciferol arm received calcium carbonate equivalent to 380 mg calcium ions and 500 mg calciferol per 24 h. Those allocated to sulindac received 300 mg sulindac per 24 h. All medication was coded so that both doctors and patients were unaware of treatment grouping. The code was broken only on completion of the trial.

Each group of patients took the appropriate medication for 6 months, followed by a 2-month washout period before commencement of the next medication. All patients underwent oesophagogastroduodenoscopy by one endoscopist (F.S.-C.) before the start of the trial and after each of the two treatment periods. The number of polyps was estimated and the size of the largest polyp present was measured by comparison with an open-end biopsy forceps. During each gastroscopy, biopsies of representative gastric fundal and antral as well as duodenal polyps were taken, together with biopsies of apparently 'normal' gastric and duodenal mucosa. All gross findings from gastroduodenoscopy were recorded for all patients at the start of the study as a baseline and then monthly after a course of therapy until the end of the study.

All specimens were examined histologically; mucosal proliferation indices were calculated by *in vitro* incorporation of labelled 5-bromo-2′-deoxyuridine (BrdU).

Biopsy material was deposited immediately in growth medium (10 ml growth medium contained 8·2 ml RPMI (Gibco BRL Lite Technologies, New York, USA), 0·1 ml fluorodeoxyuridine stock solution (0·2 mg/ml), 0·7 ml BrdU stock solution (3·07 mg/ml) and 1 ml fetal calf serum (FCS)). Tissues were then incubated with the mucosal side down on a wire mesh placed over a Petri dish containing growth medium. Incubation was carried out for 1 h in 95 per cent oxygen and 5 per cent carbon dioxide at 37°C. After the incubation period, the tissue was frozen in OCT (British Drug House, Poole, UK) compound and kept at −80°C until processed. Biopsies were oriented on the specimen holder and cryosectioned at a thickness of 50 μm. The slides were fixed overnight in 70 per cent alcohol at room temperature.

The slides were taken out of alcohol and air dried, and placed in sodium hydroxide 0·07 mol/l at room temperature for exactly 2 min. They were transferred to phosphate-buffered saline (PBS) at pH 8·5 for 10 min to neutralize the alkali. Sections were covered with antiBrdU-FITC (fluorescein-iso-thiocyanate) antibody (Becton and Dickinson, California, USA) in a 1:10 dilution in PBS containing 10 per cent FCS for 1 h at room temperature in a humidified chamber. Slides were washed and counterstained with propidium iodide 0·0005 mg/ml and ribonuclease 0·5 mg/ml, and coverslipped with antifade mountant. Negative controls were prepared by adding FCS instead of antibody.

Slides were examined in a laser scanning microscope (Carl Zeiss, Jena, Germany). For each biopsy at least ten (range ten to 19) longitudinally oriented crypts were studied. Optical sections

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Paper accepted 10 March 1996

of 5 μm were made through the entire crypt. The green FITC image, showing only the proliferating cells, was first obtained with a 515–545-nm band-pass filter. The orange propidium iodide image was obtained through a 565-nm long-pass filter. The two images were stored separately for every optical section. The image analysis software VIDAS (Kontron, Jena, Germany) was used for further analysis.

The propidium iodide images were used as reference to avoid attributing a proliferating cell to the adjacent crypt. They were also used to measure crypt height. Crypts were divided into lower, middle and upper thirds to determine the distribution of the proliferating cells within them. The FITC images at different optical sections for each crypt were combined by a pixelwise selection of higher grey value to obtain one final image, to avoid counting the same cell more than once.

The following mucosal proliferation indices of the biopsies taken from the stomach and duodenum of the various patients were measured:

1 Crypt height in microns.
2 Height of the proliferative compartment expressed as a percentage of the crypt height. The proliferative compartment was taken as the distance, in microns, from the bottom of the crypt to the most luminally situated proliferating cell.
3 Distribution of proliferating cells within the lower, middle and upper thirds expressed as a percentage of the total number of proliferating cells (range two to 49 cells) per crypt.

The above indices were measured for each crypt (ten to 19 crypts for each biopsy) and mean values were taken as the final reading for each biopsy.

Results

Tables 1 and *2* show, respectively, the number and size of the polyps found during baseline gastroscopy and after 6 months of treatment with sulindac *versus* calcium with calciferol. Eighteen patients enrolled in the initial phase of the study, but only 15 took sulindac and only 11 took calcium and calciferol for 6 months.

Table 1 Numbers of patients with polyps at various sites in the upper gastrointestinal tract during baseline gastroscopy and after 6 months of treatment with sulindac or calcium and calciferol

Site and no. of polyps	Baseline ($n = 18$)	Sulindac ($n = 15$)	Calcium and calciferol ($n = 11$)
Ampulla			
0	17	15	11
1–5	1	0	0
Duodenum (second part)			
0	10	8	5
1–5	3	5	2
5–10	1	0	0
> 10	4	2	4
Duodenum (first part)			
0	14	13	10
1–5	3	0	1
5–10	0	0	0
> 10	1	2	0
Antrum			
0	16	14	9
1–5	0	1	0
5–10	1	0	1
> 10	1	0	1
Fundus			
0	5	3	1
1–5	2	2	1
5–10	0	0	1
> 10	11	10	8

Thirteen patients had gastric polyps; 11 had gastric fundic glandular polyps, one of whom had gastric adenomatous polyps as well, while one patient each had only gastric hyperplastic polyps and gastric adenomatous polyps. Only 12 patients had duodenal polyps: two had hyperplastic polyps, three had both hyperplastic and adenomatous polyps, and seven had only adenomatous duodenal polyposis.

The proliferative indices for 'normal' gastric and duodenal mucosa are shown in *Tables 3* and *4* respectively. The proliferative index is the height of the proliferative compartment as a percentage of the crypt height. There was no statistical difference between any of the groups for both the stomach and duodenum when proliferative indices were compared.

There was no difference in crypt height between the groups for either stomach or duodenal mucosa.

Table 2 Number of patients with respect to polyp size at baseline endoscopy and after 6 months of treatment with sulindac or calcium and calciferol

Site and size of polyps (mm)	Baseline ($n = 18$)	Sulindac ($n = 15$)	Calcium and calciferol ($n = 11$)
Ampulla			
0	17	15	11
5–10	1	0	0
Duodenum (second part)			
0	10	8	5
1–5	8	7	6
Duodenum (first part)			
0	14	13	11
1–5	4	1	0
5–10	0	0	1
> 10	0	1	0
Antrum			
0	16	14	9
1–5	1	1	1
5–10	1	0	0
> 10	0	0	1
Fundus			
0	5	3	1
1–5	10	8	8
5–10	1	2	1
> 10	2	2	1

Table 3 Proliferative indices in 'normal' stomach mucosa at baseline and after treatment with sulindac or calcium and calciferol

	Baseline	Sulindac	Calcium and calciferol
Crypt height (μm)	276·6(19·0)	261·6(14·9)	272·6(27·5)
Proliferative index (percentage of crypt height)	55·1(3·1)	51·6(2·9)	56·0(3·1)
Distribution of proliferating cells (%)			
Lower third	58·0(2·9)	67·0(3·4)*	57·8(2·8)
Middle third	37·4(2·4)	29·6(2·4)†	33·5(4·0)
Upper third	4·5(1·1)	3·3(1·4)	4·3(1·1)
Change in proliferative compartment height (%)	—	− 4·9(4·1)	1·2(5·3)

Values are mean(s.e.m.). *$P<0{\cdot}05$, †$P<0{\cdot}03$ (sulindac *versus* baseline, paired *t* test)

Table 4 Proliferative indices in 'normal' duodenal mucosa at baseline and after 6 months of treatment with sulindac or calcium and calciferol

	Baseline	Sulindac	Calcium and calciferol
Crypt height (μm)	361·5(16·1)	373·0(29·7)	360·1(29·2)
Proliferative index (percentage of crypt height)	50·6(3·3)	55·6(3·2)	48·1(2·7)
Distribution of proliferating cells (%)			
Lower third	69·2(4·5)	58·8(4·6)*	70·0(4·4)
Middle third	28·1(3·8)	35·8(3·1)†	28·9(4·1)
Upper third	2·6(1·0)	5·2(2·9)	1·1(0·6)
Change in proliferative compartment height (%)	—	1·6(4·8)	−2·3(3·2)

Values are mean(s.e.m.). $^*P<0·05$, $^†P<0·03$ (sulindac *versus* baseline, paired *t* test)

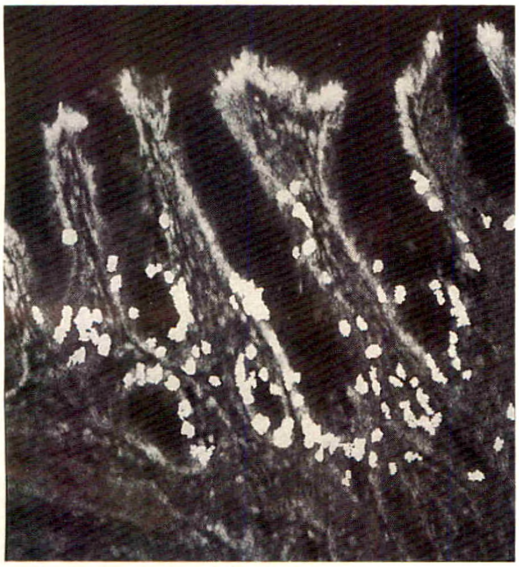

Fig. 1 Crypts in the stomach with proliferating cells extending beyond the upper two-thirds of the crypts

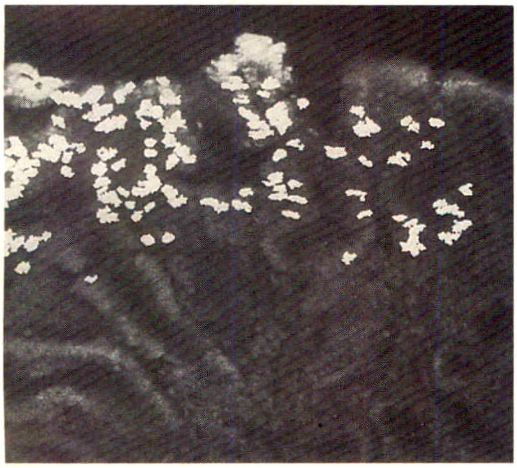

Fig. 2 Crypts in the duodenum with proliferating cells at the luminal end, showing a shift towards the lumen

Calcium with calciferol had no noticeable effect on the proliferative index or on the distribution of proliferating cells within normal gastric (*Fig. 1*) or duodenal (*Fig. 2*) mucosa. Although sulindac did not affect normal duodenal mucosa to any noticeable extent, it tended to stabilize normal gastric mucosa by shifting the proliferative zone downwards, i.e. towards the lower third compared with baseline findings and calcium with calciferol, reaching statistical significance for the lower and middle zones of gastric crypts.

Discussion

NSAIDs may control the proliferation of cell growth and therefore decrease carcinogenesis. NSAIDs have been found useful in some patients with metastatic carcinoma, head and neck cancer, and desmoid tumours[9–12,16]. The mechanism for sulindac-induced inhibition of cell proliferation is believed to be a reduction in the level of prostaglandins E_2 and $F_{2\alpha}$, which are thought to increase cellular proliferation by raising the levels of adenosine 3′,5′-cyclic monophosphate and other messengers of growth regulation or by increasing tumour angiogenesis[18].

In cell culture, the omission of NSAID was followed by a return of growth patterns that existed before exposure to the drug. In addition, inhibited DNA synthesis returned to control levels after the drug was stopped. Administration of NSAIDs prevented this overactive drive towards tumour formation, reducing it to that of normal cells.

The inhibitory effects of dietary calcium have been seen in rectal epithelial proliferation in patients with FAP[19]. Calcium may exert its antitrophic effect on colorectal mucosa by binding to free bile acids and fatty acids that would otherwise stimulate cell damage and regeneration[8,20]. It also reduces the dihydroxy bile acid concentration in duodenal bile. This implies that calcium binds to phosphate in the small intestine and that the calcium phosphate complex binds luminal bile acids. Calcium reduces the crypt cell proliferation rate in rat and human colonic cell lines.

Vitamin D inhibits *in vitro* cell proliferation in rectal tissue from patients with FAP. The presence of vitamin D_3 receptors within normal and malignant colorectal tissues, together with increased colonic absorption of calcium after small bowel resection, suggests that the colon could be a target organ for vitamin D_3. It acts as a differentiating agent and some of these actions are associated with modulation of receptor concentration[8]. Calciferol is able to switch cellular activity from proliferation to differentiation[7,8,21,22]. In premalignant conditions associated with accelerated epithelial cell proliferation, a reduction in crypt cell proliferation rate might decrease the risk of malignant transformation.

This study shows that there was a reduction in the crypt proliferation index of the gastric epithelium from patients who were given sulindac. The distribution of proliferating cells in the upper and middle thirds of the crypt was reduced following treatment with sulindac compared with baseline values.

However, administration of sulindac did not reduce the number or size of polyps. This may be because of the short duration of the study and perhaps may also be due to the small number of patients studied, although other studies have shown that polyp regression may occur in less than 4 months[9–11]. Another reason may be that the inhibitory effect of sulindac on cell proliferation is lost as polyps enlarge[23].

Contrary to a previous report on the effectiveness of sulindac on duodenal mucosal proliferation[18], this study showed no response in duodenal mucosa compared with stomach mucosa. In duodenal mucosa, calcium and calciferol decreased the proliferative compartment compared with sulindac, whereas sulindac had greater effects on gastric mucosa. This may be an important consideration for patients with FAP as upper gastrointestinal instability may result in malignancy.

In conclusion, sulindac may be useful in patients with FAP, but further trials involving a larger population are needed to confirm this theory. Calcium with calciferol is probably not useful as prophylaxis against the development of upper gastrointestinal cancer in patients with FAP.

Acknowledgements

This study was supported in part by a grant from the Singapore Cancer Society. The authors thank Stephanie Fook Chong from the Department of Clinical Research, Singapore General Hospital, for help with statistical analysis.

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British Journal of Surgery 1996, **83**, 1767–1768

Surgical workshop

Parallel self-expanding covered metal stents in the trachea and oesophagus for the palliation of complex high tracheo-oesophageal fistula

J. P. M. ELLUL, R. MORGAN*, D. GOLD, J. DUSSEK†, R. C. MASON and A. ADAM*

*Departments of General Surgery, †Thoracic Surgery and *Interventional Radiology, Guy's Hospital, London SE1 9RT, UK*

Correspondence to: Mr R. C. Mason

Palliation of oesophageal carcinoma consists mainly of the treatment of dysphagia. However, 5 per cent of patients with oesophageal cancer also develop a fistula between the oesophagus and trachea. The symptoms of aspiration are devastating and are difficult to treat with low morbidity. Untreated, most patients die from a combination of respiratory infection and starvation[1]. Recently, covered expanding metal stents have been shown to be an excellent treatment for oesophageal fistula and perforation[2,3], and seem to be more effective than conservative treatment, plastic tubes or surgical bypass treatment methods. However, patients who present with a high tracheo-oesophageal complex fistula adjacent to the cricopharyngeal sphincter are particularly difficult to treat. A method is described that enables control of high tracheo-oesophageal fistulas.

Surgical technique

Patient 1

A 62-year-old man was referred for palliation of a 6-cm oesophageal squamous cell carcinoma with tracheo-oesophageal fistula, 23 cm from the incisor teeth (3 cm from the cricopharyngeal sphincter). A polyurethane-covered Wallstent endoprosthesis (Schneider, Bulach, Switzerland), 25 mm in diameter and 105 mm in length, was inserted under sedation and fluoroscopic guidance as described previously[3], and a contrast swallow performed the day after insertion showed satisfactory passage of contrast medium into the distal oesophagus and no leakage into the fistula. The patient was able to eat and drink without difficulty and was discharged home. However, 1 month later he returned with recurrent symptoms of fistula. A contrast swallow confirmed a further tracheo-oesophageal fistula arising above the superior border of the stent. Endoscopy showed that there was insufficient space between the cricopharyngeus and the upper border of the previous stent to place a coaxial stent in order to cover the new fistula. Bronchoscopy performed under general anaesthesia demonstrated tumour eroding into the trachea and partially occluding the left main bronchus. Two polyurethane-covered Wallstent prostheses, each 16 mm in diameter and 55 mm long, were inserted coaxially to cover most of the trachea. A subsequent contrast swallow (*Fig. 1*) showed free passage of contrast into the distal oesophagus without leakage into the trachea. The patient was discharged home eating normally.

Paper accepted 30 June 1996

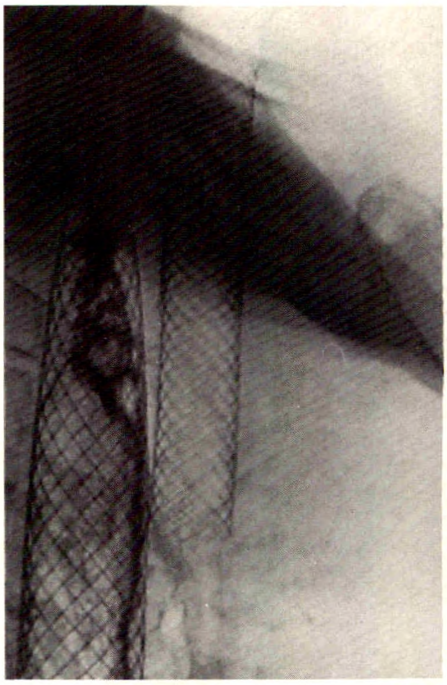

Fig. 1 Contrast swallow showing parallel stents in the oesophagus and trachea. There is no leak of contrast from the oesophagus, confirming that the high tracheo-oesophageal fistula has sealed

Patient 2

A 67-year-old woman was referred with recurrent dysphagia after treatment of a 7-cm squamous cell carcinoma of the oesophagus by radiotherapy. Endoscopy showed a tight stricture at 20 cm (1·5 cm from the cricopharyngeal sphincter) and computed tomography demonstrated appearances consistent with extramucosal recurrence of the tumour. A polyurethane-covered Wallstent endoprosthesis, 20 mm in diameter and 110 mm long, was placed, with return to normal swallowing. Some retrosternal discomfort persisted following placement of the stent. Some 3 weeks later the patient returned complaining of severe bouts of coughing. A tracheo-oesophageal fistula from the tumour at the upper end of the stent was confirmed on contrast swallow. Again, in view of the proximity of the fistula to the cricopharyngeal sphincter, a covered tracheal stent was inserted under combined endoscopic and fluoroscopic guidance. A contrast swallow the following day showed no leak into the trachea from the fistula. The patient was able to take a normal diet.

Discussion

Covered self-expanding metal stents are highly effective for the palliation of malignant tracheo-oesophageal fistula or oesophageal perforation. Placement of the stent ensures immediate sealing of the fistula and prevents further pulmonary contamination. However, fistulas close to the cricopharyngeal sphincter cannot be covered adequately by oesophageal stenting alone. Tracheal stenting seems to be preferable in this situation. Metal expandable stents are suited to placement in the trachea ecause of their flexibility and very low profile, which ffers little or no resistance to air flow. Furthermore, xpandable stents in the trachea cause the patient no iscomfort. In view of the oesophageal obstruction and ysphagia caused by the tumour, stenting of the esophagus is also necessary. The authors recommend arallel stenting as a useful procedure for the palliation of ymptoms arising from high malignant tracheo-esophageal fistula.

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British Journal of Surgery 1996, **83**, 1769–1771

Palliation of oesophageal carcinoma using the argon beam coagulator

G. S. M. ROBERTSON, M. THOMAS, J. JAMIESON, P. S. VEITCH and A. R. DENNISON

Department of Surgery, Leicester General Hospital, Leicester, UK
Correspondence to. Mr G. S. M. Robertson, Department of Surgery, Clinical Sciences Building, Leicester Royal Infirmary, Leicester LE2 7LX, UK

Oesophageal intubation occasionally fails to palliate inoperable carcinoma: some tumours are unsuitable for this procedure and others overgrow the tube. This study reports a series of nine patients (median age 79 (range 55–87) years) in whom the argon beam monopolar coagulator via a flexible endoscopic probe was used to ablate such tumours. Fourteen ablation procedures were performed. The endoscope was passed to the stomach at the end of each procedure. There were no complications; the median hospital stay was 2 (range 1–13) days. Thirteen procedures rendered the patients completely asymptomatic for a median of 6 (range 4–12) weeks. Six patients died a median of 14 (range 4–38) weeks after the first ablation, reflecting their limited life expectancy. The argon beam coagulator provides an effective alternative to laser ablation, being considerably cheaper and safer, while maintaining the minimally invasive nature of the palliation.

Oesophageal carcinoma in the Western world tends to present late, carries a poor prognosis even after 'curative' surgical resection and frequently occurs in elderly patients for whom surgical resection is inadvisable. Palliation in this situation is aimed at relieving dysphagia and maximizing the quality of the patient's remaining life.

Available methods for palliation include endoscopic intubation with rigid[1–3] or expanding metal stents[4], laser photocoagulation[5–7], photodynamic therapy[8], intraluminal brachytherapy[9] and bipolar coagulation[6]. In the authors' unit the majority of such tumours have been treated effectively by intubation[1]. However, 5–10 per cent of such tubes become occluded by tumour overgrowth[2], while some soft exophytic tumours produce dysphagia but fail to grip the tube. In such situations a neodymium yttrium–aluminium–garnet laser has been used to ablate the intraluminal tumour endoscopically[7,10].

The laser in this context is acting as an expensive heating device, coagulating tissue between 60°C and 90°C and vaporizing it when the temperature exceeds 100°C. The process of vaporization increases the risk of perforation; coagulation with subsequent sloughing and ulceration may be sufficient. While the laser is effective, the equipment is expensive to purchase and maintain, and complex to use, requiring elaborate safety precautions. The technique itself can be time-consuming, particularly for large tumours, and has an accepted rate of oesophageal perforation. Although the risk of perforation is commonly related to the process of dilatation rather than the use of the laser[11], alternative methods of delivering thermal energy to the tumour might have significant advantages.

The argon beam coagulator represents a technical improvement in monopolar electrocautery. A jet of argon rather than the conventional electrosurgical medium of air is ionized to conduct high-frequency electrical energy of uniform intensity to the target area. This clears blood from the area being cauterized and allows a no-touch technique, which provides rapid effective haemostasis and more controllable depths of dessication and thermal coagulation than conventional monopolar electrocautery[12,13].

The argon beam coagulator has been used effectively for haemostasis in areas where superficial ooze is a potential problem[14,15], and has proved to be particularly effective on parenchymal organs such as the liver[16,17], spleen[16,18–20], lung[13] and kidney[21]. Its application laparoscopically has been described[22] and its endoscopic use has been proposed[23]. Its ability to ablate tumour when used at high-power settings has also been reported[24].

This study reports the use of the argon beam coagulator for the palliative ablation of advanced oesophageal malignancy in conjunction with palliative endoscopic intubation.

Patients and methods

Over an 18-month period nine patients (four men), median age 79 (range 55–87) years, underwent 14 'episodes' of argon ablation. On 12 occasions the patient had dysphagia for all solids and on two occasions inability to swallow fluids, including saliva. Six patients had previously had Atkinson tubes inserted (one large diameter short (L/S) and five medium diameter short (M/S) Atkinson oesophageal prostheses; Olympus KeyMed, Southend, UK) and presented with recurrent dysphagia a median of 3·5 (range 1·5–9) months later. In two patients argon ablation was used before subsequent insertion of an Atkinson tube 1 month later, and in one a single argon ablation only was required. At diagnostic endoscopy the mean length of the tumour (seven adenocarcinomas and two squamous carcinomas) was 5 cm. There were two oesophageal, five gastro-oesophageal and three gastric tumours.

Each ablation was performed under general anaesthesia. Initially, a dual-channel scope (GIF 2T20, Olympus KeyMed) with an external diameter of 12·75 mm was passed, allowing aspiration of food debris above the obstruction. For tumours overgrowing the bottom of Atkinson tubes, the internal diameter of which ranged from 11·6 mm for M/S to 12·9 mm for L/S, a smaller scope (GIF XQ10; Olympus KeyMed) with a diameter of 10 mm was then used to gain access to the bottom of the tube.

A 1·5-m flexible Argon gas coagulation probe (600K0035, Soring, Medical Advance, Banbury, UK) connected via a foot switch-activated hand-piece (53-015, Soring) to an argon coagulator (ARCO-MBC, Sóring) was then passed down the endoscope. The argon component of the diathermy machine was set to a maximum of 5, giving an argon gas flow of 7 l/min and a power setting of 150 W.

The tumour was then ablated using 1–5-s bursts of clearly visible ionized argon. A technique in which chips of tumour were

Paper accepted 2 February 1996

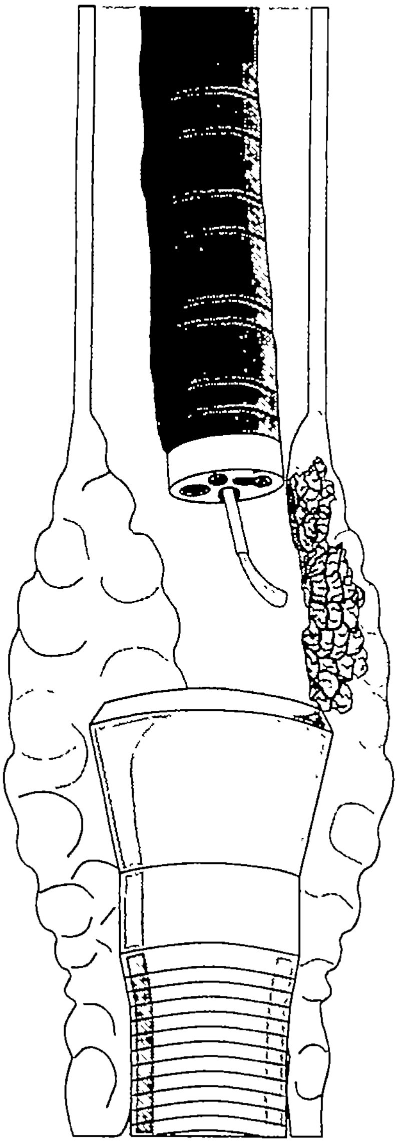

Fig. 1 Method of tumour ablation for overgrowth above an oesophageal tube using the flexible argon probe via a dual-channel endoscope. Chips of tumour are resected, progressing proximally

resected piecemeal rather than vaporized was used (*Fig 1*). When chips of tumour accumulated above the tube in proximal lesions they were pushed through the tube to allow continued visualization. Smoke created few problems as it tended to pass orally spontaneously, displaced by continued insufflation of clean air via the endoscope. The dual-channel scope allowed excess smoke to be aspirated as well, with the bridge facility allowing the argon probe to be flexed slightly when appropriate. More contact than usual between tissue and the argon probe necessitated intermittent clearing of coagulum from the flexible probe by flushing with air from a syringe. The integral alarm sounded and the equipment cut out when this was required. The ceramic tip of the probe also wore down quite quickly and was intermittently trimmed back using wire cutters.

As with laser ablation[5,7], starting distally and progressing proximally gave better visualization allowing fuller resection; it also allowed the funnel at the top of the Atkinson tube to be used as a guide to the oesophageal lumen in proximal overgrowth, permitting resection of both exophytic and submucosal intraluminal tumour. The aim was to be able to pass the scope easily through the tumour (and tube) at the end of the procedure. A chest radiograph was obtained after operation In the absence of any evidence of perforation, free fluids were allowed when the patient was alert, with normal diet the following day

Results

Three of the six patients with an Atkinson tube *in situ* had tumour overgrowing the top of the tube; in two the Atkinson tube had become displaced into the stomach and a new one was inserted under the same general anaesthetic after argon ablation; one patient had tumour occluding the lower end of the tube. Of these six patients three required two ablations and one required three, in each case for tumour regrowing in the same position. There was a median interval of 7·5 (range 4–12) weeks between ablations.

At the start of nine of the 14 ablation procedures the scope could not be passed into the stomach. In each case the scope was successfully passed to the stomach at the end of the procedure and the endoscopist was satisfied that a good lumen had been created. The median anaesthetic time for the 14 ablation episodes was 22·5 (range 15–45) min.

There were no perforations and no anaesthetic complications. The presenting dysphagia was completely relieved by all but one of the 14 procedures with the patients comfortably managing breakfast of cereals and toast the following morning, although one patient continued to experience mild dysphagia for solids. All patients left hospital, usually the next day, giving a median total duration of hospital stay of 2 (range 1–13) days.

At the time of the last follow-up or death, a median of 12 (range 4–38) weeks following ablation, only one patient had persisting dysphagia. Six of the nine patients have died since the procedure, a median of 14 (range 4–38) weeks after the first ablation.

Discussion

While not common, recurrent dysphagia following insertion of a palliative oesophageal stent is a distressing event occurring in patients with advanced malignancy and a life expectancy of weeks. Although it is possible to replace such tubes[25], this can be a traumatic procedure with a high risk of perforation. Ideally, palliation should be safe, relatively non-invasive, effective and cheap. While laser ablation fulfils some of these criteria, its potential hazards and cost as in laparoscopic surgery mitigate against it. The authors believe that the argon beam coagulator has several advantages.

In terms of safety, the beam of argon has no effect unless ionized when it sheds a whitish-blue light. This allows the path of the electric current over a distance of up to 1 cm from applicator to tissue to be clearly seen. Moreover, monopolar cautery is a modality commonly used and well understood by surgeons, and theatre staff are familiar with setting the units up on a daily basis. There is no doubt that, despite its advantages, injudicious use of the argon can result in gas embolus[26], damage to adjacent structures[27] and perforation of the bowel wall[28]. However, the depth of energy penetration is more controllable and considerably less than with laser.

The procedures were all performed under general anaesthesia as it was considered that the amount of smoke generated during ablation would be unpleasant under sedation. There is no theoretical or apparent reason to prevent ablation under sedation if general anaesthesia is contraindicated. All patients recovered rapidly from the procedure with a short hospital stay, reflecting the minimally invasive nature of the procedure.

The ablation process appeared to be highly effective and at the high-power settings used the ionized argon beam produced a rapid controllable effect on the tumour, carving channels through it under direct vision with limited conduction to underlying tissues[23] and no bleeding. The establishment of a clear passage endoscopically was a good predictor of postoperative symptomatic relief. The median duration of asymptomatic follow-up was 6 (range 4–12) weeks following the ten ablation procedures in which no new Atkinson tube was subsequently inserted.

The cost of the equipment used for argon ablation (£22 800) was considerably less than the £94 000 for the authors' therapeutic laser unit (CL-60; Sigmacon UK, Stanmore, UK). In addition, the frequent use of the argon unit further defrays the cost, making it a facility that should be available in most theatre suites.

In conclusion, while oesophageal intubation remains the palliative method of choice for inoperable oesophageal carcinoma, there are occasional tumours that overgrow the tubes or for which this procedure is not initially suitable. In these circumstances, safe effective palliation can be minimally invasively achieved by tumour ablation using the argon beam coagulator.

Acknowledgements

The authors thank Kate Radford of the Medical Illustration Department, Leicester Royal Infirmary for *Fig 1*.

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British Journal of Surgery 1996, 83, 1772–1775

Quality of life following resection of oesophageal carcinoma

H. U. ZIEREN, C. A. JACOBI, J. ZIEREN and J. M. MÜLLER

Department of Surgery, Charité, Humoldt University of Berlin, Schumann-Strasse 20/21, 10 117 Berlin, Germany
Correspondence to: Dr H. U. Zieren

Quality of life following resection of oesophageal carcinoma was assessed by patients using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and by a psychologist using he Spitzer Index. Quality of life was evaluated in 119 patients on one occasion 12 months after operation and in 30 patients regularly, starting with a preoperative assessment. Self and external evaluation showed a significant correlation ($r = 0{\cdot}61$), but quality of life was assessed as being higher by the external observer. Limited physical performance status and somatic complaints were the most important postoperative dysfunctions, whereas emotional, social and economic disorders were found to be less frequent and less severe. Of several factors analysed only tumour recurrence ($P < 0{\cdot}01$) and anastomotic stricture ($P < 0{\cdot}05$) lowered quality of life significantly. Compared with the preoperative assessment, quality of life had decreased on discharge from hospital but was restored within 6 months of operation in disease-free patients. Further studies are required to determine the impact of adjuvant therapy for quality of life in patients undergoing surgery for oesophageal cancer.

Carcinoma of the oesophagus has a poor long-term prognosis, but radical resection of the tumour still achieves the best long-term results. Only about 20 per cent of all surgically treated patients can realistically expect to be permanently cured[1,2], so the maintenance of a good quality of life during the limited survival time is he main objective of operation in the majority of patients. Unfortunately, little is known about quality of ife following resection of oesophageal carcinoma, particularly with regard to physical, emotional, social and economic dimensions. In this study quality of life after esection of oesophageal carcinoma was studied using two validated multidimensional instruments for self and external assessment of quality of life.

Patients and methods

Retrospective cross-sectional study

Over a 3-year period 119 patients, who had undergone resection of an oesophageal carcinoma and were followed in the outpatient clinic for 12 months, were studied (*Table 1*). In each patient quality of life was assessed only once. To detect ecurrence all patients underwent clinical examination, blood nalysis, endoscopy and contrast radiology of the upper gastrointestinal tract, chest radiography, ultrasonography of the bdomen and neck, and computed tomography of the chest and bdomen. Recurrence was detected in 32 patients, ten of whom had no clinical evidence of recurrent disease.

Prospective follow-up study

To determine the impact of surgery and the postoperative ourse, quality of life was assessed in each patient, 1 day before urgery, on the day of discharge from hospital and at 3-monthly intervals thereafter until the end of the first postoperative year six occasions). Over a 1-year period all patients in whom esophageal carcinoma had been resected with curative intent were studied (48 patients). Patients in whom quality of life ssessment was not complete (operative mortality, four patients; eath within 12 months, ten) were excluded. Four patients who did not meet the exclusion criteria but developed tumour recurrence within the first postoperative year were excluded from the analysis, because the retrospective study revealed that tumour recurrence decreased quality of life significantly and this subgroup of patients was too small for separate analysis. Thus, the results of the remaining 30 patients represent the postoperative course during disease-free survival (*Table 1*). Postoperative follow-up was carried out at 3-monthly intervals and included the same investigations as described above.

Table 1 Medical and sociodemographic details of patients

	12 months after operation	Follow-up study
No. of patients	119	30
Mean(s.d.) age (years)	59(9)	57(10)
Sex ratio (M:F)	90:29	21:9
Resection*		
Blunt dissection	99 (83)	26 (87)
Transthoracic resection	20 (17)	4 (13)
Oesophageal substitution*		
Stomach	106 (89)	28 (93)
Colon	13 (11)	2 (7)
Adjuvant treatment*		
Postoperative radiotherapy	33 (28)	0 (0)
None	86 (72)	30 (100)
Tumour recurrence*		
No	87 (73)	30 (100)
Yes	32 (27)	0 (0)
Anastomotic stricture*		
None	87 (73)	23 (77)
Fibrotic before quality of life assessment	21 (18)	7 (23)
Fibrotic at the time of assessment	9 (8)	7 (23)
Malignant	2 (2)	0 (0)
Marital status*†		
Single or living alone	35 (29)	8 (27)
Married or living with partner	84 (71)	22 (73)
Employment status*†		
Employed full time	36 (30)	15 (50)
Temporarily disabled	17 (14)	2 (7)
Retired	49 (41)	10 (33)
Housekeeping	17 (14)	3 (10)

*Values in parentheses are percentages; †number at the time of single assessment, or before surgery in patients in the follow-up study

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Paper accepted 11 February 1996

Operative procedures

All patients underwent R_0 resection of squamous cell carcinoma or adenocarcinoma of the thoracic or abdominal oesophagus by transhiatal or transthoracic three-phase McKeown-type[3] oesophagectomy. Where possible, a gastric tube was used for oesophageal replacement. If the stomach was not suitable because of previous surgery, a colonic segment was used as an oesophageal substitute. All anastomoses between the proximal oesophagus and the gastric or colonic substitute were performed in the neck by a one-layer technique described previously[4]. Patients were discharged from hospital when they were able to eat, a median of 14 days after operation. Thirty-three patients in the postoperative study received adjuvant postoperative radiotherapy between 6 and 12 weeks after surgery. As postoperative radiotherapy failed to improve survival[5], no patient in the follow-up study received adjuvant treatment.

Quality of life assessment

Quality of life was assessed both by the patients and by a psychologist. Self-assessment was performed using the German translation of the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer (EORTC) as published in 1987[6,7]. Some of the 36 questions are aggregated to obtain scales of different dimensions of the quality of life: 'physical function', 'role function', 'emotional function', 'social function', 'cognitive function', 'global quality of life', 'financial impact' and several disease symptoms. As intended by the developers of the questionnaire, four disease-specific questions (difficulty in swallowing, loss of weight, fullness following meals, and heartburn) were added. The external assessment was performed by a psychologist after an interview with the patient and was based on the well validated quality of life index developed by Spitzer and co-workers[8,9]. The Spitzer Index registers quality of life in the categories of activity, daily living, health, support and outlook using a predefined three-level scale for each category. The global quality of life index can range from 0 to 10, with a higher score indicating a better quality of life.

Statistical analysis

The data were stored by means of the database program dBase III Plus (Ashton Tate, Maidenhead, UK) and analysed with the software package BMDP (BMDP Statistical Software, Los Angeles, California, USA). Symptom and functional scores of the questionnaire were linearly transformed such that results ranged from 0 to 100. For univariate analysis to identify possible influencing factors, individual subgroups were compared with the Kruskal–Wallis test. Correlation among individual variables was tested by cross-table analysis using Kendall correlation coefficient. Significance was assumed at the 5 per cent level ($P<0{\cdot}05$).

Results

Twelve-month retrospective study

The most frequent functional limitations reported by the patients were related to physical and role function. Some 105 (88 per cent) of the 119 patients could not perform strenuous activities, like moving heavy furniture, 82 (69 per cent) could not run a short distance, 37 (31 per cent) had trouble taking a long walk, 23 (19 per cent) had to spend most of the day indoors or in a bed or a chair (13 per cent), 13 (11 per cent) had trouble walking a short distance, and two (2 per cent) needed help with eating, dressing, washing or using the toilet (physical function). Thirty-seven patients (31 per cent) considered that they had no restriction in their job or household tasks (role function), and 67 (56 per cent) reported a partial and 15 (13 per cent) a complete incapacity. Compared with these somatic limitations, dysfunction in emotional, social and financial areas was significantly less common and rated as less severe. Nevertheless, 33 per cent of the patients suffered from emotional disturbances such as anxiety or depression, although only 6 per cent rated them as severe. No restrictions in social life or financial situation were reported by 73 and 81 per cent of the patients respectively, and only 3 per cent each felt very limited in these areas. The mean(s.d.) score of global quality of life was 55(18) (median 50, range 0–100). The global ratings of health status and quality of life showed a similar distribution on the original seven-point scale (*Fig. 1*).

Fatigue was the most severe disease symptom, from which 81 patients (68 per cent) suffered to various degrees. Besides fatigue, about half the patients had varying degrees of difficulty in swallowing (54 per cent of patients), sleep disturbance (48 per cent), pain (46 per cent), lack of appetite (46 per cent), dyspnoea (45 per cent) and loss of weight (44 per cent), but only 14 per cent (sleep disturbance) to 19 per cent (loss of appetite) rated these symptoms as severe Less frequent were symptoms such as fullness following meals (36 per cent), concentration disturbances (33 per cent), nausea and vomiting (27 per cent), heartburn (19 per cent), diarrhoea (11 per cent) and constipation (9 per cent).

External assessment according to the Spitzer Index (Fig. 2). The median rating of quality of life corresponded to the second highest score of the Spitzer Index (9 points).

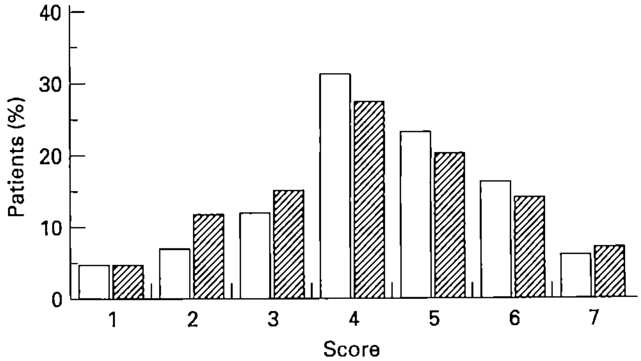

Fig. 1 Self-rating of global health status (▨) and global quality of life (☐) according to the Quality of Life Questionnaire, from 1 ('very poor') to 7 ('excellent')

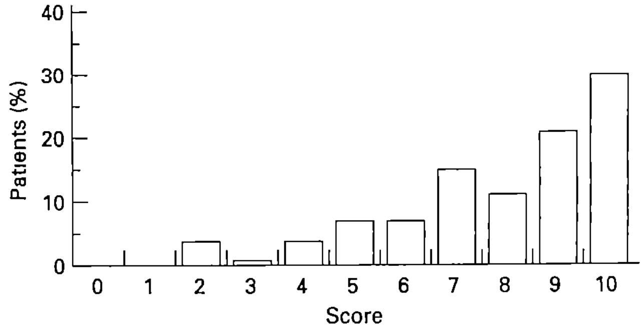

Fig. 2 Quality of life assessment by a psychologist using the Spitzer Index A higher score represents a higher quality of life

Correlation between different dimensions of quality of life. There was a significant correlation ($r=0{\cdot}61$) between the self-rating of global quality of life according to the questionnaire and the external assessment according to the Spitzer Index. Between these global measures and the single scales and symptoms of the questionnaire, similar correlations were determined (*Table 2*). Except for the financial impact, all other scales and symptoms correlated significantly with the global assessment of quality of life. The highest correlation was found for the fatigue scale, indicating that this symptom has a high impact on the overall sense of well-being. In contrast to this, the correlation of disease-specific symptoms such as dysphagia, postprandial fullness and heartburn with global quality of life was significant but not high. Compared with the patients' self-rating, the Spitzer Index correlated more strongly with the scales of physical and role function and less with disease-specific symptoms.

Impact of medical and sociodemographic factors. Univariate analysis revealed no significant influence on quality of life for the following factors: sex, marital status, resection procedure, type of reconstruction and previous postoperative adjuvant radiotherapy. Patients who had returned to work had a better level of physical and role function ($P<0{\cdot}01$) and suffered less from emotional disturbances ($P=0{\cdot}04$) than those who were retired. Anastomotic stricture at the time of quality of life assessment caused a significantly poorer global quality of life ($P=0{\cdot}04$), lower physical function ($P=0{\cdot}04$) and more disease symptoms ($P=0{\cdot}03$).

The most significant factor in quality of life was tumour recurrence. Patients with symptomatic recurrent disease had a significantly lower self and external rating of global quality of life ($P<0{\cdot}01$), had lower levels in physical ($P<0{\cdot}01$), role ($P<0{\cdot}01$) and emotional ($P=0{\cdot}03$) function, and suffered more from disease symptoms ($P<0{\cdot}01$) than disease-free patients. However, disturbances related to social areas ($P=0{\cdot}09$) and financial aspects ($P>0{\cdot}1$) were not significantly increased by tumour recurrence. Patients in whom tumour recurrence was asymptomatic at the time of quality of life assessment had a significantly lower self-assessed global quality of life ($P<0{\cdot}05$) and suffered more from emotional disturbances ($P<0{\cdot}05$) than disease-free patients. However, disease symptoms and the other functional scales of the questionnaire, as well as of the Spitzer Index, did not differ significantly from those of disease-free patients.

Table 2 Correlation between global ratings of quality of life and the scales and symptoms of the Quality of Life Questionnaire 12 months after operation

	Global quality of life rating*	
	Self-assessment (QLQ)	External assessment (Spitzer Index)
Fatigue	0·68	0·67
Nausea and vomiting	0·43	0·34
Physical function	0·40	0·58
Pain	0·35	0·36
Role function	0·33	0·56
Weight loss	0·33	0·32
Emotional function	0·32	0·35
Dyspnoea	0·30	0·40
Sleep disturbance	0·30	0·22
Diarrhoea or constipation	0·24	n.s.
Concentration disturbance	0·22	0·22
Difficulty in swallowing	0·22	0·14
Fullness following meals	0·19	n.s.
Heartburn	0·17	n.s
Social functioning	0·15	0·17
Financial impact	n.s.	n.s

*Sorted in descending order. QLQ, Quality of Life Questionnaire; n.s., not significant

Prospective follow-up study

The mean self-rating for the functional scales and most important disease symptoms are given in *Figs 3* and *4*. Before operation limited role functioning was the most severe restriction. Role and physical function deteriorated after surgery upon discharge from hospital and had improved again within 6–9 months after operation. Emotional, social and financial dysfunction was rated as low during the whole time period. Before surgery, dysphagia was the most frequent and severe disease symptom. While dysphagia had improved on discharge from hospital, fatigue, weight loss and pain had increased. Within 3 months after surgery these symptoms had improved again, and after 12 months were rated as lower than before operation. Self and external assessment of global quality of life showed a similar course, with a significant deterioration immediately after surgery and a recovery within 3–6 months afterwards. Some 12 months

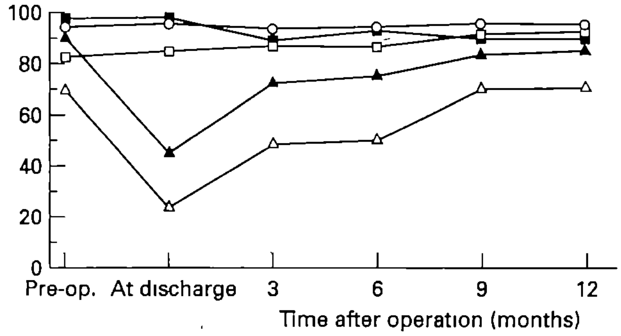

Fig. 3 Self-rating of functional scales and the financial aspect of the Quality of Life Questionnaire during the follow-up study. A higher score represents a higher level of functioning: ▲, physical; △, role, □, emotional; ○, social; ■, financial

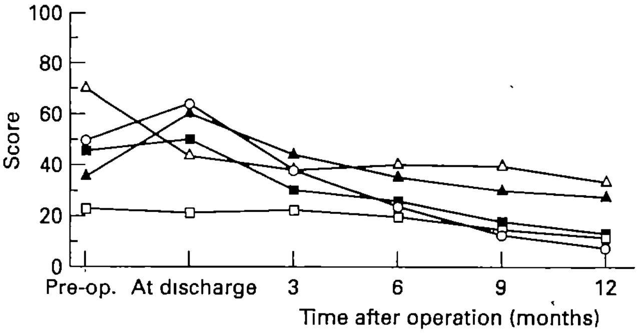

Fig. 4 Self-rating of the most important disease symptoms of the Quality of Life Questionnaire during the follow-up study. A higher score represents a higher level of symptomatology: ▲, fatigue; △, dysphagia; ■, pain; □, nausea and vomiting; ○, weight loss

after surgery, global quality of life was slightly higher than before operation. Eight patients developed fibrotic anastomotic strictures; they had a lower global quality of life and suffered more from disease symptoms ($P < 0{\cdot}05$) than those without such a stricture. After successful endoscopic dilatation of the strictures, quality of life and physical complaints recovered rapidly and did not then differ from those in patients without strictures.

Discussion

In agreement with other studies[10,11], the detailed assessment of quality of life in various domains revealed that quality of life after resection of oesophageal carcinoma is primarily impaired by physical limitations and disease symptoms. Although emotional and social dysfunction was less frequent, these components were found to have a significant influence on the evaluation of overall quality of life. Self-rating and external assessment showed a significant correlation but quality of life was scored higher by the external observer. Because the methods used for self and external assessment were different in this study, the results of these assessments are not strictly comparable. Blazeby and co-workers[12] compared patients' and doctors' quality of life assessments using the Quality of Life Questionnaire in patients with oesophageal cancer and noted that the agreement between doctor and patient was poor for all functional scales and only fair for some symptom scales. The authors therefore concluded that valid measures of quality of life must come from patients themselves.

Tumour recurrence was the most important factor determining postoperative quality of life. Patients who had no clinical evidence of recurrent disease differed from disease-free patients only in that they evaluated their global quality of life worse and indicated more emotional dysfunction. Therefore, it can be concluded that the depression resulting from the diagnosis of tumour recurrence will have an important impact on patients' quality of life assessment and that the decreasing quality of life in those with recurrent disease will be increased by emotional disturbances. Ruckdeschel *et al.*[13], who investigated quality of life in patients with bronchogenic carcinoma using the Functional Living Index – Cancer[14], found such a close correlation between quality of life and tumour recurrence that quality of life was said to be a significant predictor for overall and disease-free survival.

While anastomotic stricture significantly decreased quality of life, the rather frequently reported difficulty in swallowing as well as other digestive discomforts such as heartburn or postprandial fullness correlated only poorly with the ratings of global quality of life, as was also the case in another study[11]. This is probably due to the fact that most postoperative difficulties in swallowing and eating can be overcome by chewing well and adapting the diet, and that only manifest strictures lead to malnutrition and fatigue and ultimately decrease quality of life. Most anastomotic strictures observed were benign and could be treated readily by endoscopic bouginage. Therefore, such strictures affected quality of life much less than tumour recurrence, and quality of life improved again after successful therapy of these strictures. As the patients had been informed about the possible occurrence of these harmless strictures before surgery, they were not associated with increased anxiety or depression.

The Quality of Life Questionnaire proved to be a practical tool for measuring quality of life in surgical patients. Meanwhile the EORTC has produced a revised version of the questionnaire, in which six questions have been deleted[15]. As patients included in this study represent a highly selected group of all those with oesophageal carcinoma, further studies are required to analyse quality of life in patients with advanced disease, who will be treated by palliative or multimodal adjuvant therapy, e.g. neoadjuvant radiochemotherapy, and to compare the results of such measures with the results obtained by surgery alone.

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British Journal of Surgery 1996, 83, 1776–1778

Impact of splenectomy on circulating immunoglobulin levels and the development of postoperative infection following total gastrectomy for gastric cancer

T. FUJITA, K. MATAI, S. KOHNO and K. ITSUBO

First Department of Surgery, Jikei University School of Medicine, 3-25-8 Nishishinbashi, Minato-ku, Tokyo 105, Japan
Correspondence to: Dr T Fujita

Splenectomy increases the postoperative morbidity of total gastrectomy for carcinoma of the stomach. The reasons for this increased risk of postoperative infection are unknown. The aim of this study was to evaluate the impact of splenectomy on circulating immunoglobulin levels and to determine whether splenectomy was an independent risk factor for the development of postoperative infection in 154 patients undergoing total gastrectomy for carcinoma of the stomach. Splenectomy reduced circulating immunoglobulin M levels in the early postoperative period following total gastrectomy. However, it was not identified as an independent risk factor for the development of postoperative infection by multivariate analysis.

Splenectomy adversely affects postoperative morbidity and mortality resulting from sepsis following gastrectomy for carcinoma of the stomach[1–3]. However, the mechanisms whereby splenectomy raises the risk for the development of postoperative infection are unknown[3,4]. In addition to removing particulate antigen and bacteria from the bloodstream, the spleen plays a central role in host defence against infection by the production of antibodies and opsonins and by the recruitment of complement[5,6]. The short-term effect of splenectomy on circulating immunoglobulin levels in patients with carcinoma has not been examined.

The aim of this study was to evaluate the impact of splenectomy on circulating immunoglobulin levels and to determine whether splenectomy is an independent risk factor for the development of postoperative infection following total gastrectomy for carcinoma of the stomach.

Patients and methods

Impact of splenectomy on circulating immunoglobulin levels

Between January 1993 and July 1994, 20 consecutive patients who underwent curative total gastrectomy for adenocarcinoma of the stomach were studied after giving informed consent. Curative resection was defined as that in which there was no residual macroscopic disease after surgery. Each tumour was located in the proximal or middle portion of the stomach, or in the whole stomach. In all patients the second tier of lymph nodes (N_2), beyond the perigastric nodes (N_1)[7], was removed. Of these patients, ten underwent *en bloc* resection of the spleen with or without the distal pancreas, depending on the location and size of the tumour and the preference of the surgeon. All total gastrectomy procedures were accompanied by Roux-en-Y reconstruction with a 40–50-cm loop of jejunum. None of the 20 patients died from postoperative complications. Serum samples were obtained from each patient both before and on days 1, 3, 7 and 14 after operation to measure circulating levels of immunoglobulins and the third component of complement.

Data are presented as mean(s.d.) Statistical analysis was performed with the Mann–Whitney *U* test. $P < 0.05$ was considered significant.

Impact of splenectomy on the development of postoperative infection

Between January 1983 and December 1992, 154 patients underwent total gastrectomy with curative intent for carcinoma of the stomach. Splenectomy was not performed in 84 patients, and in 70 splenectomy with or without distal pancreatectomy was carried out. Each patient's notes were reviewed to obtain clinicopathological data including postoperative infection. The variables obtained were age, sex, preoperative serum level of albumin, duration of operation and estimated peroperative blood loss. The addition of splenectomy or distal pancreatectomy to total gastrectomy was compared in patients who had a postoperative infection and those who did not.

To determine the significance of any difference between the means of the different measurements, Student's *t* test was used according to variance equivalence. Categorical data in the two groups were evaluated with the χ^2 test. For multivariate discriminant analysis, each continuous variable was correlated with the development of postoperative infection by univariate χ^2 analysis to select a single cutoff point that maximized statistical significance but preserved clinical utility. Thus all variables were entered in multivariate discriminant analysis as categorical variables with the two categories (0, absent or normal; 1, present or abnormal). These factors were then weighted to construct the single discriminant function that best maximized the multivariate *F* ratio and minimized the Wilks λ value[8]. A statistical package (Multivariate Analysis III; IBC, Miyazaki, Japan) was used for multivariate discriminant analysis. Differences were considered significant at $P < 0.05$.

Results

Immunoglobulin levels

There were no differences in age, male:female sex ratio, serum albumin concentration on admission, estimated blood loss during surgery or duration of surgery between patients who underwent splenectomy and those who did not, as shown in *Table 1*. Neither was there any significant difference in stage of disease[7] between the two groups (stage I, three; stage II, three; stage III, four, in patients undergoing splenectomy *versus* stage I, six; stage II, one; stage III, three, in patients having no splenectomy).

Preoperative serum levels of immunoglobulin (Ig) G, IgA and IgM in each group were not statistically different. Although splenectomy did not influence postoperative circulating levels of IgG and IgA, IgM levels on days 7

Paper accepted 8 February 1996

Table 1 Patient details

	Total gastrectomy with splenectomy	With no splenectomy
No. of patients	10	10
Age (years)*	61·0(13·3)	62·9(7·4)
Sex ratio (M:F)	4:6	6:4
Preoperative serum albumin concentration (g/dl)*	4·1(0·3)	4·1(0·3)
Estimated blood loss (ml)*	472·1(197·6)	503·3(210·0)
Duration of surgery (min)*	275·1(46·7)	253·4(37·7)

*Values are mean(s.d.)

Table 2 Changes in serum immunoglobulin levels in patients undergoing total gastrectomy with or without splenectomy

	Serum immunoglobulin level (mg/dl)		
	IgG	IgA	IgM
Before operation			
Splenectomy	1195·0(139·7)	245·0(74·3)	106·7(15·2)
No splenectomy	1066·0(141·8)	244·4(60·3)	113·0(47·4)
After operation			
Day 1			
Splenectomy	983·3(101·4)	194·7(41·6)	91·3(5·4)
No splenectomy	875·0(125·7)	241·5(63·5)	93·7(22·5)
Day 3			
Splenectomy	812·5(169·8)	188·5(42·3)	76·0(·6·9)
No splenectomy	808·0(190·5)	235·8(90·1)	90·2(20·3)
Day 7			
Splenectomy	910·0(154·1)	224·2(23·7)	83·3(9·3)
No splenectomy	916·7(135·5)	321·2(103·5)	114·3(18·3)*
Day 14			
Splenectomy	1400·0(277·8)	371·3(110·6)	104·3(14·3)
No splenectomy	1316·7(248·1)	450·5(168·7)	159·8(33·0)*

Values are mean(s.d.). Ig, immunoglobulin. $^*P<0{\cdot}05$ (splenectomy *versus* no splenectomy, Mann–Whitney U test)

Table 3 Results of univariate analysis

	Infection	No infection	$P\dagger$
Age (years)*	59·9(8·5)	58·4(12·5)	n.s
Preoperative serum albumin concentration (g/dl)*	3·9(0·4)	4·1(0·4)	n.s.
Duration of surgery (min)*	326·8(109·5)	300·4(60·9)	n.s
Estimated blood loss (ml)*	896·0(1077·8)	463·5(349·8)	<0·01
Percentage of patients who underwent splenectomy	80	39	<0·01
Percentage of patients who underwent distal pancreatectomy	45	16	<0·01

*Values are mean(s.d.). n.s., Not significant. †Student's t or χ^2 test

Table 4 Results of multivariate analysis

	F	P
Blood loss of more than 600 ml during surgery	5·59	<0·05
Distal pancreatectomy	2·62	n.s.
Splenectomy	1·85	n.s.

n.s., Not significant

and 14 after surgery were significantly ($P<0{\cdot}05$) lower in patients who underwent splenectomy than in those who did not (*Table 2*). No statistical difference was found between the two groups in preoperative and postoperative serum levels of the third component of complement.

Risk factors for postoperative infection

The overall postoperative mortality rate was 4 per cent (six patients). It was 2 per cent after total gastrectomy alone and 6 per cent after total gastrectomy with splenectomy (P not significant). Postoperative infection not accompanied by anastomotic leakage occurred in 6 per cent of patients who underwent total gastrectomy alone. This incidence was significantly ($P<0{\cdot}01$) lower than the 24 per cent observed in patients who underwent total gastrectomy with splenectomy. Amongst the postoperative infections, there was no statistical difference in the incidence of wound infection and intra-abdominal abscess between the two groups. However, the incidence of postoperative pneumonia was 10 per cent in patients who underwent splenectomy in addition to total gastrectomy, this being significantly ($P<0{\cdot}02$) higher than the 1 per cent in those who underwent total gastrectomy alone. Anastomotic leakage was identified in 2 per cent of patients who underwent total gastrectomy alone, and in 8 per cent of those who underwent total gastrectomy with splenectomy. This difference was not statistically significant. Although it seemed that splenectomy increased the risk for postoperative infection, stage of the disease was more advanced and preoperative serum levels of albumin were lower in patients who had splenectomy. Furthermore, mean(s.d.) intraoperative blood loss was much greater in patients undergoing splenectomy (714·6(702·4) ml with splenectomy *versus* 397·6(282·3) ml without splenectomy, $P<0{\cdot}01$).

Eight patients who had anastomotic leakage were excluded from the study because such leakage was considered an intraoperative technical failure rather than a result of postoperative infection. The analysis of risk factors for postoperative infection was therefore performed in 146 patients, of whom 20 had postoperative infection. *Table 3* shows the results of the univariate analysis of the risk factors for postoperative infection. Of the six variables analysed, intraoperative blood loss, splenectomy and distal pancreatectomy were significantly correlated with the development of postoperative infection. Of these three factors, the multivariate discriminant analysis identified operative blood loss greater than 600 ml (*Table 4*). Addition of splenectomy or distal pancreatectomy to total gastrectomy was not independently associated with the development of postoperative infection.

Discussion

The spleen makes up 25 per cent of the total lymphoid mass and is an important component of the reticuloendothelial system[9]. The adverse effects of splenectomy on immune function, such as reduced response to pneumococcal antigen[10] and attenuated ability of hepatic Kupffer cells to opsonize particulate matter[11], are well recognized. Furthermore, long-term depression of T cell proliferation has been reported in patients after splenectomy for trauma[12]. In this study, splenectomy did not alter the circulating levels of IgG, IgA and the third component of complement, but it reduced IgM levels on days 7 and 14 after total gastrectomy in patients with gastric carcinoma These findings are in keeping with those of Schumacher[13], who found that serum levels of IgM were significantly lower in childhood after splenectomy than in those with no splenectomy, despite no differences in IgG and IgA levels between the two groups Another study showed that splenectomized calves were slow to produce IgM in response to infection with *Anaplasma marginale*[14]. The low circulating levels of IgM afer splenectomy suggest that the spleen contributes relatively more IgM than IgG and IgA to the total serum immunoglobulin content. An alternative explanation is that the spleen stimulates IgM production by other lymphoid tissues.

Postoperative infection occurred more commonly in patients who had splenectomy than in those who did not (24 *versus* 6 per cent). However, splenectomy was not found by multivariate analysis to be an independent risk factor for the development of postoperative infection following total gastrectomy. These results are not consistent with those of Brady *et al.*[1], who performed multivariate analysis and found that splenectomy was independently predictive of infectious complications following gastrectomy for carcinoma of the stomach and that the odds ratio for complications in patients undergoing splenectomy was 1 73 compared with those without splenectomy. Another study[3] showed that the addition of splenectomy led to an increase in operative mortality and postoperative morbidity rates following gastrectomy for carcinoma of the stomach for the same stage of disease. However, these studies did not consider the impact of intraoperative blood loss or blood transfusion on the development of postoperative infection

In the present study the only independently significant variable associated with the development of postoperative infection was blood loss of more than 600 ml during surgery when infection was entered as the outcome variable into the multivariate discriminant analysis. Excessive blood loss during surgery leads the patient to be transfused with blood products Homologous blood transfusion is considered to be immunosuppressive, but the association of infection with homologous blood transfusion has not been clear[15]. A relationship between blood transfusion and infectious complications after surgery for gastric[16] or colorectal[17] cancer has recently been shown. In addition, Duke *et al*[18] reported that total blood transfusion was the only independent factor associated with the development of perioperative infection in patients suffering splenic injury, despite the lack of association between splenectomy and infectious complications by multivariate analysis. An attenuation in the host defence mechanism following blood transfusion might facilitate the development of postoperative infection during the postoperative period following total gastrectomy for gastric cancer, but splenectomy was found not to be an independent risk factor for the development of postoperative infection.

Although the present authors agree with others[1,3,19–22] that routine splenectomy should be abandoned in the course of gastrectomy for carcinoma of the body and cardia, because it does not adversely influence the outcome of patients with gastric cancer, splenectomy should still be strongly considered when the primary tumour is located in the upper body along the greater curvature or in the fundus. To diminish the incidence of postoperative infection after total gastrectomy with splenectomy for gastric cancer, attempts should be made to minimize operative blood loss and transfusion requirements.

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British Journal of Surgery 1996, 83, 1779–1781

High prevalence of *Helicobacter pylori* infection in duodenal ulcer perforations not caused by non-steroidal anti-inflammatory drugs

E. K. W. NG, S. C. S. CHUNG, J. J. Y. SUNG*, Y. H. LAM, D. W. H. LEE,
J. Y. W. LAU, T. K. W. LING†, W. Y. LAU and A. K. C. LI

*Departments of Surgery, *Medicine and †Microbiology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong*
Correspondence to: Professor A. K. C. Li, Department of Surgery, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

There has been controversy regarding the relationship between *Helicobacter pylori* and perforated peptic ulcer, which is known to have a high recurrence rate if only simple patch repair is performed. The aim of this study was to evaluate the association between *H. pylori* infection and intake of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with perforated duodenal ulcers. Of the 73 patients recruited over a 16-month period, 51 (70 per cent) had evidence of *H. pylori* infection by intraoperative gastroscopy and antral biopsies. The infection rate rose to 80 per cent if NSAID users were excluded. The *H. pylori*-infected group was significantly younger (mean 47·6 *versus* 62·5 years), with a male preponderance (49 of 51 *versus* 14 of 22 patients), and had significantly less NSAID consumption (three of 51 *versus* ten of 22) and more prolonged dyspepsia (40 of 51 *versus* ten of 22), compared with *H. pylori*-negative patients. *H. pylori* infection probably plays an important role in the causation of non-NSAID-induced duodenal ulcer perforation. Whether eradication of the bacteria can alleviate the strong ulcer diathesis in this subgroup of patients is unknown.

Helicobacter pylori is recognized as a major causative factor of peptic ulcer disease[1,2]. Eradication of the bacteria is effective in hastening healing and reducing ulcer relapse[3–5]. Whether eradication of *H. pylori* can prevent recurrent ulcer complications is unconfirmed[6]. There is growing evidence that successful eradication of *H. pylori* reduces recurrent ulcer bleeding[7,8]. However, data regarding *H. pylori* in peptic ulcer perforation remain scanty; the infection rate ranges from 47 to 80 per cent[9,10]. This study aimed to evaluate prospectively the relationship between *H. pylori* infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with perforated duodenal or prepyloric peptic ulcers.

Patients and methods

Patients

Between September 1994 and December 1995 all patients diagnosed as suffering from perforated peptic ulcers and admitted to this unit were asked to give consent for recruitment into the study. Demographic data, history of dyspepsia of more than 3 months, previous ulcer-related complications and the use of NSAIDs were recorded at the time of admission. Exclusion criteria were recent intake of antibiotics or acid-suppressing treatment (H_2-receptor antagonists or proton pump inhibitors) and clinical features suggestive of spontaneous sealing of perforations and no requirement for operation. Patients with perforated gastric ulcers were also excluded.

Procedures

All patients were resuscitated before surgery. Intravenous cefuroxime (bolus injection of 1·5 g) was administered at the time of anaesthetic induction. No acid-suppressing treatment was prescribed before operation. When perforated duodenal or prepyloric ulcers were confirmed by either laparotomy or laparoscopy, intraoperative flexible peroral gastroscopy was performed. Antral biopsies were taken as follows: one for a rapid urease test (*Campylobacter*-like organism (CLO) test, Delta West, Bentley, Western Australia, Australia), three for bacterial culture and three for histological examination. Omental patch repair was then performed unless there were indications for definitive acid-reducing surgery. For patients in whom gastrectomy was contemplated, no intraoperative endoscopy was carried out. Tissue biopsies of the antrum were sampled from the resected specimen immediately after operation. Peritoneal toilet was performed in all patients before wound closure.

Microbiological culture

The biopsy specimens were transported in calf brain–heart solution at room temperature. On arrival in the laboratory, they were minced and cultured on Columbia agar (Oxoid, Basingstoke, UK) supplemented with 5 per cent horse blood at 37°C for 5 days under microaerophilic conditions. The presence of *H. pylori* was confirmed by morphological analysis of the colony, Gram staining and biochemical tests (for oxidase, catalase and urease).

Histological examination

Three pieces of antral biopsies were fixed with 10 per cent formalin. Haematoxylin and eosin staining was then performed and histological evidence of *H. pylori* sought by experienced pathologists unaware of the CLO test and culture results.

Patients were defined as positive for *H. pylori* infection when two of the three tests showed presence of the bacterium. Positivity of the CLO test alone was not considered adequate for the diagnosis of *H. pylori* infection. The overall prevalence of infection was calculated. The association between *H. pylori* infection status and NSAID consumption as well as a history of prolonged dyspepsia were determined with Fisher's exact test. Student's *t* test was used to assess the effect of age on prevalence of *H. pylori* infection and NSAID consumption in this group of patients.

The study was approved by the institutional ethics committee.

Results

During the 16-month study period 89 patients were admitted with a perforated peptic ulcer. Endoscopy was not performed in 16 patients: eight required preoperative intensive care stabilization and were considered too ill for

Paper accepted 12 July 1996

intraoperative endoscopy, three refused to give consent for biopsy, and equipment failure was encountered in the other five (failed endoscope insertion through the cricopharyngeus, two; failure of air insufflator, two; breakdown of light source, one).

A total of 73 patients were successfully enrolled into the study (*Table 1*). There was a male preponderance and a median age of 51 (range 19–86) years. Simple repair (either laparoscopic or a conventional open approach) was performed in 62 patients, and truncal vagotomy with pyloroplasty in three. The three patients who underwent vagotomy had a long-standing history of peptic ulcer. Two of these patients also had a past history of ulcer complications. In the remaining eight patients partial gastrectomy was required to obtain secure closures (all these ulcer perforations were larger than 1·5 cm in diameter and were too big for simple patch repair). The overall perioperative mortality rate of the studied group was 7 per cent (five of 73 patients).

Of the 73 patients with tissue biopsies available, 51 (70 per cent) had evidence of *H. pylori* infection (*Table 2*). Thirteen patients (18 per cent) had a history of NSAID consumption: three had *H. pylori* infection and ten were *H. pylori* negative. The incidence of *H. pylori* infection was 80 per cent (48 of 60) in patients not using NSAIDs. The NSAID consumption rate was significantly higher in the *H pylori*-negative group than in patients with *H. pylori* infection ($P<0{\cdot}001$). *H. pylori*-infected patients also had a significantly higher prevalence of prolonged dyspepsia (more than 3 months) than those with no infection ($P<0{\cdot}02$). There was no difference in mean(s.d.) age with regard to NSAID consumption (60·2(18·0) *versus* 50·4(15·1) years, $P=0{\cdot}055$). However, patients infected with *H pylori* were significantly younger than those with no infection (mean(s.d.) 47·6(15·7) *versus* 62·5(18·4) years, $P<0{\cdot}01$). There was also a significant male preponderance in the *H. pylori*-infected group (*Table 1*) ($P<0{\cdot}001$).

Table 1 Demographic data of patients admitted to the study

	Endoscopy	
	Performed	Not performed
No. of patients	73	16
Median (range) age (years)	51 (19–86)	72 (36–87)
Sex ratio (M:F)	63:10	10:6
Type of ulcers		
Duodenal	69	15
Prepyloric	4	1
NSAID use		
Yes	13	4
No	60	12
Other		
ICU care	2	8
Equipment failure	0	5
No consent	0	3

NSAID, non-steroidal anti-inflammatory drug; ICU, intensive care unit

Table 2 Comparison of variables between patients positive and negative for *Helicobacter pylori* infection

	Helicobacter pylori		
	Positive	Negative	*P*
No. of patients	51	22	
No. taking NSAIDs	3	10	<0 001*
No. with dyspepsia	40	10	<0·02*
Mean(s.d.) age (years)	47·6(15·7)	62·5(18·4)	<0·01†
No of men	49	14	<0·001*

*χ^2 test, †Student's *t* test

Discussion

Perforated duodenal ulcer is a common surgical emergency. Simple omental patch repair results in recurrent ulceration in up to 42 per cent of patients[11,12]. Recurrent perforation, despite continuous acid-suppressing therapy, has also been reported[13]. The conventional surgical approach includes acid-reducing procedures, such as partial gastrectomy or truncal vagotomy with gastric outflow drainage[14]. With the advent of potent acid-suppressing agents like H_2 antagonists and proton pump inhibitors, more patients are treated with simple patch repair and maintained on long-term acid-suppressing drugs[15]. In the past decade *H. pylori* has been recognized as an important causative agent for uncomplicated peptic ulcers[1,2]. Eradication of *H. pylori* has been proven to be effective in hastening ulcer healing and preventing recurrence[3,4]. As there is increasing evidence that eradication of *H pylori* can prevent recurrent peptic ulcer bleeding[7,8], it would be interesting to see whether the same efficacy can be demonstrated in perforated ulcers.

Thus far there are conflicting results from studies on the association between perforated duodenal ulcers and *H. pylori*. Reinbach *et al.*[9] reported a low prevalence of *H. pylori* infection, only 47 per cent, in a series of 80 patients with acute duodenal ulcer perforations. This rate of infection is not significantly higher than that in the general population. The authors concluded that *H. pylori* infection may not play an important role in the causation of ulcer perforation.

In contrast Sebastian *et al.*[10] reported *H. pylori* infection in 24 of 29 patients. Thus, while Sebastian and colleagues recommend antibiotic therapy to eradicate *H. pylori* in all patients with duodenal ulcer perforation, Reinbach *et al.* claim that perforated ulcers may have a different pathogenesis. Although both reports targeted patients with the same disease, the two studies are not truly comparable. In Reinbach *et al.*'s series over 40 per cent were receiving NSAIDs, whereas in the other series only one patient was known to be taking such an ulcerogenic drug before admission. The mean age of the two groups of patients was also significantly different.

In the present study 70 per cent of patients with perforated duodenal or prepyloric ulcers were infected with *H pylori*. This is not much higher than the prevalence of infection in the local population (55 per cent)[16], and is obviously lower than would be expected among all patients with duodenal ulcer. However, by subclassifying these patients according to the usage of NSAIDs, 80 per cent (48 of 60) of non-NSAID-related perforations were seen to be infected by *H. pylori*, compared with only three of 13 in NSAID users. Thus, among non-NSAID users, *H. pylori* infection is probably an important cause of ulcer formation and perforation. Moreover the observation that patients with *H. pylori* infection had a significantly higher incidence of prolonged dyspepsia supports chronicity rather than acute disease.

On the other hand, NSAID users are more likely to be suffering from acute ulcer and perforation due to the ulcerogenic effect of the drugs. Conceivably, a history of chronic dyspepsia is less common in these patients.

Perforated duodenal ulcers are likely to result from diverse causes, of which *H. pylori* and NSAID use are the two major ones. The discrepancy between the data of Sebastian *et al.*[10] and Reinbach and co-workers[9] can be explained by the fact that the former group was studying mainly patients with ulcers resulting from chronic *H. pylori* infection, whereas Reinbach *et al.*'s patients had acute ulcers related to the use of NSAIDs. Although *H. pylori* infection and the use of NSAIDs are not mutually exclusive in the causation of peptic ulcers, many reports have suggested that they are independent risk factors with different ulcerogenic mechanisms[17,18].

Currently, the treatment of perforated peptic ulcer is not ideal. Acid-reducing surgery is associated with significant perioperative mortality and long-term morbidity rates, especially in the elderly[19]. On the other hand, patients maintained on continuous acid-suppressing agents may still develop recurrent ulcer, sometimes even with complications. Furthermore, the cost of prolonged maintenance treatment is considerable. Certainly the recent introduction of laparoscopic repair for perforated duodenal ulcers has made the issue even more controversial[20,21]. As curing *H. pylori* infection has been shown to reduce the recurrence of non-NSAID-related duodenal[22] and gastric[23] ulcers, the present authors recommend antimicrobial therapy to eradicate *H. pylori* infection in patients suffering from perforated peptic ulcers not caused by NSAID usage, especially young men with a long history of dyspepsia or proven ulcers. However, whether eradication of *H. pylori* alone, without surgical or medical acid suppression, would alter the ulcer diathesis in this subgroup of patients and reduce the number of recurrent ulcers is still unknown.

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British Journal of Surgery 1996, 83, 1782

Case report

Abnormal suntanning following transthoracic endoscopic sympathectomy

M. S. WHITELEY, S. B. RAY-CHAUDHURI and R. B. GALLAND

Department of Surgery, Royal Berkshire Hospital, London Road, Reading RG1 5AN, UK
Correspondence to: Mr R B Galland

Transthoracic endoscopic sympathectomy (TES) has become the method of choice for treating patients with palmar hyperhidrosis. There are few complications reported with this procedure. A complication not described previously is reported here.

Case report

A 23-year-old man was referred with palmar and axillary hyperhidrosis There was a history of asthma and hayfever, for which he took beclomethasone and salbutamol inhalers. He was otherwise well In July 1995 he underwent bilateral TES by means of the two-port technique[1]. On each side, a diathermy hook was used to breach the pleura and identify T2, T3 and T4 ganglia. These ganglia were lifted clear of the thoracic wall and divided using the diathermy hook.

Fig. 1 Back of patient showing absence of suntan in sympathectomized skin

Paper accepted 25 January 1996

At outpatient review 4 weeks later, the patient commented on a 'tide-mark' on the front and back of his black T-shirt and a deficiency in his suntan above this level (*Fig. 1*). The shirt showed that the patient was sweating up to the T4 dermatome but no higher, proving the efficacy of the sympathectomy. He had a normal suntan up to the T4 dermatome but not in the area above this point.

The patient confirmed that he had been sunbathing immediately after the operation but had not used any lotion on his skin. Some 12 weeks after the operation, after further sunbathing, the difference in skin colour had almost disappeared. His hands were still completely dry.

Discussion

TES is a well tolerated, minimally invasive technique for treating palmar and axillary hyperhidrosis[2,3]. Side-effects include compensatory sweating (55–70 per cent) and a 10 per cent reduction in heart rate. Complications are uncommon, occurring in 1–2 per cent of patients and including haemothorax, pneumothorax and Horner's syndrome, which may be either permanent or transient.

Initially, it was suspected that the use of sunblock could have caused this difference in tanning. The skin still able to sweat would have washed the cream away allowing the ultraviolet light through to the skin, while the dry skin would have remained protected. The patient confirmed that he had not used any such cream, however.

There is a link between the sympathetic nervous system and skin pigmentation, as shown in vitiligo[4] and leprosy[5]. This link may explain the changes described in this case.

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British Journal of Surgery 1996, 83, 1783–1787

Surgical care in octogenarians

A. BUFALARI, M. FERRI, P. CAO*, R. CIROCCHI, R. BISACCI and L. MOGGI

*Department of Surgery and Surgical Emergencies, University of Perugia and *Unit of Vascular Surgery, Perugia, Italy*
Correspondence to: Dr A Bufalari, Dipartimento di Chirurgia ed Emergenze Chirurgiche, Sezione di Chirurgia Generale e Vascolare, Policlinico, Monteluce, Via Brunamonti, 06122 Perugia, Italy

The general surgical profile of octogenarians compared with that of younger patients, and risk factors predictive of operative mortality and morbidity, were determined retrospectively using a computer database for all patients admitted between 1989 and 1993. There were 934 admissions of octogenarians and surgery was performed in 447 cases (47·9 per cent). The admission rate of patients over 80 years of age increased during the 5-year period from 4·6 to 9·0 per cent, and was significantly higher than that of geriatric patients aged 65–79 years ($P<0·01$). Emergency admissions (63·6 per cent) and operations (42·3 per cent) were more frequent in patients aged over 80 years ($P<0·01$); emergency operations increased during the 5 years from 38 to 59 per cent. Altogether, 83 deaths and 171 complications were recorded. The mortality rate of octogenarians was greater than that of younger patients ($P<0·01$). Postoperative mortality and morbidity rates were 10·1 and 32·2 per cent respectively. After multiple logistic regression analysis with stepwise backward elimination, an American Society of Anesthesiologists score of II–V ($P<0·01$), the presence of two associated diseases ($P<0·01$) and laparotomy procedures ($P<0·03$) appeared to be independent risk factors for postoperative mortality and morbidity.

In industrialized countries the number of individuals over 80 years of age is expected to increase from 7 to 10 per cent of the population. Consequently, by the year 2000, more than 50 per cent of all hospitalized patients will be of geriatric age[1–4]. The rapidly increasing number of patients, the high incidence of associated diseases, the limited functional reserve, the frequency of acute surgical problems and the high cost of healthcare warrant consideration of surgery in octogenarians[3,5]. Numerous studies have been published on the surgical problems of this older age group, but only a few involve a period of time long enough to provide prospects of healthcare needs[1,4] and examine a large enough number of patients to ensure statistical reliability[1]. Other studies have focused on specific branches of surgery[6–8] or have dealt with surgical procedures that were disparate or specialized, such as orthopaedic, otorhinolaryngological and neurosurgical[5]. Moreover, data in the literature on mortality, morbidity, risk factors, and the number and type of admissions are not always compared with those in the same period for patients younger than 80 years of age.

The aim of this study was to define the probability of operative mortality, morbidity and duration of hospitalization in different clinical settings, to focus on surgical problems in a large number of patients over 80 years of age over a 5-year period, and to evaluate trends in admissions to a general surgical department. The clinical profile of such patients is compared to that of geriatric and younger patients.

Patients and methods

A computer database established in 1989 was used to retrieve relevant information from all admissions from 1989 to 1993 The following parameters were assessed: age, sex, date of admission, type of admission (emergency or elective), type of procedure, treatment, medical or surgical complications, main surgical diagnosis on discharge, and death. In addition, in patients over 80 years of age, clinical data regarding the main surgical disease, its benign or malignant nature, and any significant concomitant disease were also recorded. Surgical intervention in the peritoneal cavity (laparotomy), excluding hernias, and surgery of the digestive system were included as additional variables. All deaths occurring within 30 days of surgery were recorded. The physiological status of octogenarians scheduled for elective surgery was evaluated in a routine programme including blood analysis, chest radiography, electrocardiography, echocardiography and cardiac evaluation, respiratory tests, clearance of creatinine, Doppler ultrasonographic examination of peripheral vessels, and clinical examination by a geriatric specialist to confirm the presence of underlying disease. Each patient was classified before operation by an anaesthetist according to the physical status classification of the American Society of Anesthesiologists (ASA).

Associated diseases such as hypertension, arrhythmia, angina, chronic obstructive pulmonary disease, endocrine and metabolic disorders were defined as present if the patient was receiving specific drug therapy. Myocardial infarction or other cardiac diseases were assessed as abnormalities on electrocardiographic and echocardiographic examination A serum level of creatinine greater than 2·0 mg/dl or the use of dialysis was indicative of renal dysfunction. Central nervous system disease was diagnosed if cerebral vascular accident, transient ischaemic attack or neurological deficit was detected on clinical examination. The presence of hepatic disease was based on levels of total bilirubin exceeding 3 0 mg/dl, alkaline phosphatase higher than 375 units/l and aspartate aminotransferase of more than 45 units/ml

Statistical analysis

Results are expressed as mean(s.d.) or as a proportion. Univariate analysis was with the χ^2 test (with Mantel–Haenszel correction), analysis of variance or the Kruskal–Wallis test for non-parametric data. $P<0·05$ was considered significant. To determine predictors of mortality and morbidity, multivariate analysis with stepwise backward elimination was used $P<0·05$ was accepted as significant for each additional variable.

Results

Clinical details

Patients. A total of 934 admissions of patients aged 80–99 (mean(s.d.) 83·6(3·3)) years was evaluated. The general characteristics of the study population are shown in *Table 1.* Men represented 52 per cent of the study

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Paper accepted 12 March 1996

population with a mean(s.d.) age of 83·2(3·0) years, significantly lower ($P<0·01$) than that of the women (84·1(3·0) years). On subdividing the patients into two age groups[9], 633 (67·8 per cent) patients were 80–84 years of age and 301 (32·2 per cent) were 85 years or more.

Admissions. *Table 2* reports the number of admissions in the 5-year study period, both in absolute numbers and percentages of the total number of admissions. In 1989 the admission of octogenarians was only 4·6 per cent of total admissions; during the 5 years the proportion increased to 9·0 per cent in 1993. In the same period admissions of geriatric (65–79 years) patients rose from 26·0 to 33·9 per cent, a lesser rise than in the octogenarians ($P<0·01$).

Table 1 General characteristics of 934 admissions and 447 operations in octogenarians

	Admissions	Operations
Mean(s.d.) (range) age (years)	83·6(3·3) (80–99)	
Age group (years)		
80–84	633 (67·8)	321 (71·8)
≥85	301 (32·2)	126 (28·2)
Sex		
M	486 (52·0)	237 (53·0)
F	448 (48·0)	210 (47·0)
Therapy		
Surgery	447 (47·9)	
Other	487 (52·1)	
Disease		
Non-malignant	762 (81·6)	339 (75·8)
Malignant	172 (18·4)	108 (24·2)
Concomitant disease		
Yes	694 (74·3)	353 (79·0)
No	240 (25·7)	94 (21·0)
Death		
Yes	83 (8·9)	45(10·1)
No	851 (91·1)	402 (89·9)
Complications		
Yes	171 (18·3)	144 (32·2)
No	763 (81·7)	303 (67·8)
Mean(s.d.) hospital stay (days)	9·7(8·4)	8·0(6·7)
ASA grade		
II		303 (67·8)
III		124 (27·7)
IV		18 (4·0)
V		2 (0·4)
Surgery		
Elective	340 (36·4)	258 (57·7)
Emergency	594 (63·6)	189 (42·3)
Laparotomy		
Yes		239 (53·5)
No		208 (46·5)
Digestive		
Yes		157 (31·5)
No		290 (64·9)

Values in parentheses are percentages. ASA, American Society of Anesthesiologists

Table 2 Admission according to age from 1989 to 1993

	Age (years)			
Year	≥80	65–79	<65	Total no. of patients
1989	136 (4·6)	764 (26·0)	2034 (69·3)	2934
1990	141 (5·1)	770 (28·0)	1838 (66·9)	2749
1991	179 (6·0)	842 (28·0)	1983 (66·0)	3004
1992	234 (7·9)	891 (30·2)	1824 (61·9)	2949
1993	244 (9·0)	925 (33·9)	1556 (57·1)	2725

Values in parentheses are percentages

Diseases. The most frequent cause of admission was vascular disease with 246 cases (26·3 per cent), and the second most common was colorectal disease (*Table 3*). Evaluation of 172 (18·4 per cent) admissions for malignant diseases shows a different distribution according to sex (*Table 4*). The group indicated as 'others' shows a greater incidence of malignant neoplasia among women because this category includes cancer of the female genitalia (five cases) and thyroid neoplasia (four cases), which was not observed in men.

Associated disease. Associated diseases are shown in *Fig. 1*, ranked by frequency, the total number (1016) of which reflects the possible occurrence of two or more diseases in the same patient. Of the 447 patients who underwent surgery, 353 (80·0 per cent) had an associated disease. The incidence was significantly higher ($P<0·01$) in the operated patients than in those who did not have an operation (342 of 487; 70·2 per cent).

Table 3 Cause of admission in 934 octogenarians, and operations performed

	Admissions			
	Total ($n=934$)	Men ($n=486$)	Women ($n=448$)	Operations ($n=447$)
Vascular	246 (26·3)	139 (28·6)	107 (23·9)	168 (68·3)
Colorectal	195 (20·9)	100 (20·6)	95 (21·2)	76 (39·0)
Stomach	115 (12·3)	48 (9·9)	67 (15·0)	33 (28·7)
Biliary tract	98 (10·5)	34 (7·0)	64 (14·3)	41 (42)
Urological	98 (10·5)	78 (16·0)	20 (4·5)	22 (22)
Abdominal wall	65 (7·0)	39 (8·0)	26 (5·8)	55 (85)
Trauma	22 (2·4)	14 (2·9)	8 (1·8)	2 (9)
Breast	17 (1·8)	0 (0)	17 (3·8)	17 (100)
Chest	17 (1·8)	11 (2·3)	6 (1·3)	5 (29)
Skin	17 (1·8)	8 (1·6)	9 (2·0)	10 (59)
Pancreas	16 (1·7)	8 (1·6)	8 (1·8)	7 (44)
Other	28 (3·0)	7 (1·4)	21 (4·7)	11 (39)

Values in parentheses are percentages

Table 4 Admissions for malignant disease in 172 octogenarians in whom 108 operations were performed

	Admissions			
	Total ($n=172$)	Men ($n=85$)	Women ($n=87$)	Operations ($n=108$)
Colorectal	44 (25·6)	26 (31)	18 (21)	36 (82)
Stomach	38 (22·1)	15 (18)	23 (26)	23 (61)
Urological	23 (13·4)	21 (25)	2 (2)	7 (30)
Breast	15 (8·7)	0 (0)	15 (17)	15 (100)
Biliary tract	10 (5·8)	3 (4)	7 (8)	3 (33)
Pancreas	9 (5·2)	4 (5)	5 (6)	7 (78)
Chest	8 (4·7)	4 (5)	4 (5)	2 (25)
Skin	7 (4·1)	5 (6)	2 (2)	6 (86)
Other	18 (10·5)	7 (8)	11 (13)	9 (50)

Values in parentheses are percentages

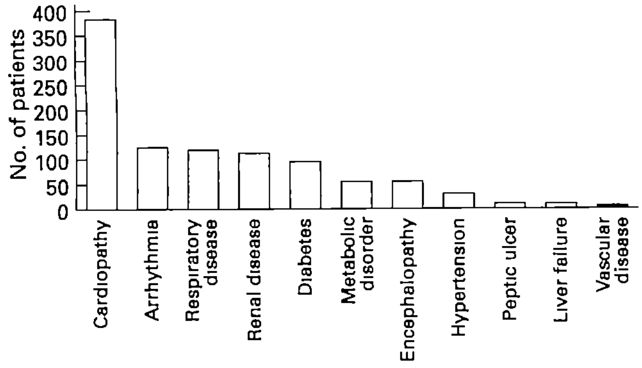

Fig. 1 Concomitant disease in 934 octogenarians admitted to the surgical department

Surgical operations. Of the 934 admissions, operation was performed in 447 cases (47·9 per cent); the ratio between operation and admissions increased from 0·38 in 1989 to 0·59 in 1993 ($P<0·01$). The general characteristics of the 447 octogenarians who underwent surgery are reported in *Table 1*. The numbers of admissions and operations are shown in *Table 5*.

Mortality. The mortality rate of octogenarians was 8·9 per cent (83 patients), with no difference in the mean(s.d.) age of survivors and non-survivors (83·6(3·2) *versus* 83·8(3·4) years respectively). This rate is higher than that recorded for patients younger than 65 years and for geriatric patients aged 65–79 years (*Table 6*). There were 45 deaths (10·1 per cent) in the operated patients over 80 years and 38 (7·8 per cent) in the non-operated (P not significant, univariate analysis).

Table 7 reports postoperative mortality and morbidity rates in relation to the principal variables. Univariate analysis revealed that emergency operations for malignant disease, laparotomy procedures and an ASA score of II–V were all prognostic variables of mortality. Multivariate analysis identified the surgical operation ($P<0·03$), an

Table 5 Elective and emergency admissions and operations in different age groups

Age (years)	Admissions	Operations		
		Total	Elective	Emergency
≥80	934	447 (47·9)	258 (57·7)*	189 (42·3)*
65–79	4192	2880 (68·7)	2131 (74·0)	749 (26·0)
<65	9235	6307 (68·3)	4929 (78·2)	1378 (21·8)

Values in parentheses are percentages *$P<0·01$ (age over 80 years *versus* age 65–79 and less than 65 years, χ^2 test)

Table 6 Overall mortality in different age groups

Age (years)	Total	Operated	Non-operated
<65	45 (0·5)	31 (0·5)	14 (0·5)
65–79	96 (2·3)	71 (2·5)	25 (1·9)
>80	83 (8·9)*	45 (10·1)*	38 (7·8)

Values in parentheses are percentages *$P<0·01$ (age over 80 years *versus* age 65–79 and less than 65 years, χ^2 test)

Table 7 Postoperative mortality and morbidity in octogenarians

	No. of patients ($n=447$)	Mortality	*P*		Morbidity	*P*	
			Univariate	Multivariate		Univariate	Multivariate
Sex							
M	237	26 (10·9)	n.s.	n.s	76 (32·1)	n.s.	n.s.
F	210	19 (9·0)			68 (32·4)		
Age (years)							
80–84	321	29 (9·0)	n.s.	n.s.	100 (31·2)	n.s.	n.s
>84	126	16 (12·6)			44 (34·9)		
Disease							
Non-malignant	339	124 (36·6)	<0·01	n.s.	103 (30·4)	n.s.	n.s.
Malignant	108	47 (43·5)			41 (40·0)		
Associated disease							
Yes	353	40 (11·3)	n.s.	<0·01*	130 (36·7)	<0·01	<0·01
No	94	5 (5)			14 (15·1)		
Type of operation							
Elective	258	4 (1·6)	<0·01	n.s.	58 (22·5)	<0·01	n.s.
Emergency	189	41 (21·7)			86 (45·5)		
Surgery							
Laparotomy	239	31 (12·9)	0·02	<0·03	99 (42·8)	<0·01	<0·01
Other	208	14 (6·7)			45 (20·8)		
Site of disease							
Digestive tract	157	21 (13·3)	n.s.	n.s.	68 (43·3)	<0·01	n.s
Other	290	24 (8·3)			76 (26·2)		
ASA score							
II	303	10 (3·3)	<0·01†	<0·01	70 (23·1)	<0·01†	<0·01
III	124	24 (19·3)			60 (48·3)		
IV	18	9 (50)			12 (67)		
V	2	2 (100)			2 (100)		

Values in parentheses are percentages. ASA, American Society of Anesthesiologists; n.s., not significant. *$P<0·01$ for two and $P<0·02$ for three associated diseases; †Kruskal–Wallis test

Table 8 Length of hospital stay related to operation and outcome

	Length of hospital stay (days)	
	Total	Operated
Operation		
Yes	12·7(9·5)*	
No	6·9(5·7)	
Death		
Yes	7·9(10·5)†	8·4(11·2)*
No	9·9(8·0)	13·2(9·2)
Complications		
Yes	15·0(10·5)*	16·5(12·9)*
No	8·5(6·5)	10·9(6·8)

Values are mean(s.d.). *$P<0·01$, †$P=0·03$ (yes *versus* no, Kruskal–Wallis test)

ASA score of II–V, the presence of two associated diseases and laparotomy ($P<0·01$) as independent prognostic factors for postoperative mortality (*Table 7*).

Morbidity. The main complications in surgical patients were cardiac disease (myocardial infarction, heart failure and arrhythmia), pulmonary disease and wound infection. Of the 487 non-operated patients, 30 (6·1 per cent) had complications during hospitalization, most of which were due to cardiac events. The significant prognostic factors on univariate analysis are shown in *Table 7*. On multivariate analysis, only the ASA score, the presence of concomitant disease ($P<0·01$ for two associated diseases and $P<0·02$ for three) and laparotomy were independently prognostic of morbidity (*Table 7*).

Duration of hospitalization. The mean(s.d.) length of hospital stay for all admissions was 9·7(8·4) days. In the 447 patients undergoing surgery, hospital stay was significantly longer than in the 487 non-operated patients ($P<0·01$). There was no significant change in the length of hospital stay over the 5 years. The appearance of complications in hospital resulted in a significant increase ($P<0·01$) in mean stay (*Table 8*) in surviving patients. Death in hospital reduced the mean(s.d.) duration of the stay compared with that in surviving patients overall (7·9(10·5) *versus* 9·9(8·0) days; $P=0·03$, Kruskal–Wallis test) and in the operated patients (8·4(11·2) *versus* 13·2(9·2) days, $P<0·01$).

Discussion

Demographic changes in Western countries have had an impact on surgery, with increased numbers of admissions and operations in geriatric patients. Among these, octogenarians represent the group with the highest increase and incidence of concomitant disease, with a limited functional reserve and a need for specific care.

It is often difficult to establish a clear-cut indication for surgery in these patients because greater risks are involved, while benefits, in terms of quality and quantity of future life, are not always predictable. In past decades this has been interpreted in a restrictive sense, thus avoiding major surgical procedures[10], but many authors have recently maintained that age *per se* should not be the sole factor for determining surgical treatment[1,3,5–9]. Octogenarians may overcome surgery, recuperate and survive as long as their peers[11]. The main focus should be to select the patients accurately by knowledge of the principal risk factors associated with complications and death.

The data from the literature on current surgical issues in octogenarians are often biased or incomplete. Nevertheless, Reiss *et al.*[9] reported that 7·5 per cent of admissions in 1989 were octogenarians, with an initial figure of 0·7 per cent in 1972 and an intermediate value of 4·1 per cent in 1982. In the present study the proportion of octogenarians was 4·6 per cent in 1989 and 9·0 per cent in 1993; the increase observed was greater than in other geriatric patients (*Table 2*). From these data it is possible to infer that the increase in surgical admission of geriatric patients (those over 65 years) relates in great part to patients older than 80 years, and increased from 15·0 per cent in 1989 to 20·8 per cent in 1993.

The majority of admissions were emergencies (63·6 per cent), a value significantly higher ($P<0·01$) than that in patients aged under 65 years (16·0 per cent) and those of 65–79 years (22·2 per cent). This has been confirmed by others who reported that emergency admissions of octogenarians vary from 50 to 67 per cent[1,3,5,9], showing a clear tendency to postpone surgery in these patients until complications or deterioration require treatment.

Among the causes for admission, vascular diseases are not frequently reported in the literature because they are considered as requiring specialist treatment[4], only major vascular surgical procedures are evaluated[3], or they are considered as a part of cardiosurgical disease[12]. In the present study vascular disease was the main cause of admission (26·3 per cent) in both men (28·6 per cent) and women (23·9 per cent), which corresponds with the values of 17 and 34 per cent reported in the literature for patients over 80 years[1,9].

The incidence of tumours increased with age and was responsible for one-third of admissions in the geriatric population. The present data show that malignant disease had an incidence of 18·4 per cent, lower than that (31 per cent) reported by Rørbaek-Madsen *et al.*[4] in a 1-year study; they did not, however, report admissions for vascular disease.

Nearly half the octogenarians admitted were operated on, in broad agreement with other reports[1,4,9,13]. Operability was lower than in patients younger than 80 years (*Table 5*), probably because of a tendency in Italy to admit octogenarians before assessing the exact nature of the disease and the indication for surgery. Nevertheless, in the present patients there was a considerable increase in operability during the 5-year study, ranging from 38 per cent in 1989 to 59 per cent in 1993, in line with data in the literature[1,4,9]. Considering these values together, the operability for malignant disease was 62·8 per cent, analogous to that reported by Rørbaek-Madsen *et al.*[4].

After surgery the mortality rate varies from 6·1 to 16·5 per cent[1,3,4,9,12–14], and appears to increase after emergency surgery compared with elective operation. Based on univariate analysis, Reiss *et al.*[9] showed that six parameters correlated significantly with postoperative mortality: age over 85 years, emergency surgery, ASA score of IV or V, laparotomy procedure, malignant disease in advanced stage, and peritonitis or a gangrenous bowel. Univariate analysis of the present patients confirms some of these observations but not all were independently valid. ASA score of II–V, the presence of two associated diseases and laparotomy remained as prognostic factors of a fatal outcome.

The morbidity of all admissions over 80 years (18·3 per cent) reported in this study is lower than that of Williams *et al.*[1] (41 per cent) and Rørbaek-Madsen *et al.*[4] (28 per cent), although postoperative complication rates were similar (32·2 and 33 per cent respectively). On multivariate analysis the independent variables that influenced the appearance of postoperative complications were the same as those for mortality: an ASA score of II–V, two or more associated diseases and laparotomy (*Table 7*).

Surgical admission of geriatric patients, in particular octogenarians, has a greater economic impact on hospital costs than that of younger patients[1,3]. The main factors contributing to increased costs in the present patients were postoperative complications, clinical emergency and associated disease. This calls for, when possible, preoperative selection of patients who may undergo surgery with a successful outcome, and suggests alternative procedures for the others. Scheduled surgery, when the disease is still under control and after a functional preoperative evaluation, can be well tolerated by patients aged over 80 years, allowing for a quality and quantity of future life similar to that of other octogenarians[5].

Acknowledgements

The authors greatly appreciate Dr S. Ricci's comments on the statistical analysis and Dr B. Sensi for help in the preparation of this manuscript.

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British Journal of Surgery 1996, 83, 1788–1791

Preoperative risk assessment in elective general surgery

H. P. KLOTZ, D. CANDINAS, A. PLATZ, A. HORVÀTH, D. DINDO, R. SCHLUMPF and F. LARGIADÈR

Department of Surgery, Division of Visceral Surgery, University of Zurich Hospital, Ramistrasse 100, CH-8091 Zurich, Switzerland
Correspondence to: Dr H P Klotz

Despite improved surgical techniques there is still a risk of mortality in elective general surgery. In a prospective study preoperative data from 3250 patients were collected and compared with postoperative systemic complications, using univariate χ^2 analysis. Highly significant ($P<0.00001$) variables were subjected to stepwise logistic regression analysis. The severity of operative procedure, higher American Society of Anesthesiologists (ASA) grade, symptoms of respiratory disease and malignancy were found to be significant risk factors predicting postoperative morbidity ($P<0.05$). Using these four variables, a simple preoperative risk scoring system has been defined. Class A (up to 5 points) was defined as a low-risk group (systemic complication rate 5·0 per cent), class B (5–7 points) was intermediate risk (systemic complication rate 17·9 per cent) and class C (8–10 points) was high risk (systemic complication rate 33·3 per cent). Patients at high risk for perioperative and postoperative complications are more likely to be identified by this analysis than by using the ASA classification alone.

Despite improved surgical technique and intensive medical care, elective procedures, including general surgery, still carry a minimal risk of mortality[1,2]. Various attempts have been made to predict the morbidity of operative procedures, with special focus on a predefined group of patients at a presumed high risk[2–5]. In addition several techniques for preoperative risk assessment have been developed, with regard to pulmonary, cardiac or other complications[6–8]. No simple bedside risk scoring system for any perioperative or postoperative complication, including individual patient data as well as weighting details of the planned elective operation, has yet emerged. The present study was initiated with the aim of defining significant risk factors that affect the postoperative outcome in elective general surgery.

Patients and methods

Study design

In 1988 a prospective study was commenced to evaluate risk factors in elective general surgery[9]. Patients were eligible for the study if undergoing an elective procedure under general or spinal anaesthesia. Only the first operative procedure during the same hospital stay was considered. A patient who was operated on more than once during the same hospital stay was counted as one single case, and the preoperative study data were documented only once, before the first intervention. Patients re-entering the hospital for a second operation after a variable time were documented as new cases The study end-points were the date of hospital discharge (no time limit) or of death in hospital Patients eligible for the study were examined the day before operation. The variables listed in *Table 1* were collected using a bedside data sheet Data collected before operation were correlated with postoperative systemic complications, including pulmonary, cardiac, septic or thromboembolic events, urinary tract infection and other complications (*Table 2*).

Patient characteristics

From 1 January 1988 to 31 December 1992, 3250 patients were studied (1750 men and 1500 women of mean(s.d.) age 52(16·8) years). Some 2994 patients (93·2 per cent) drank 20 g alcohol or less each day and 217 (6·7 per cent) drank more than 20 g alcohol daily (data missing from 39 patients). Some 1940 (60·6 per cent) were non-smokers, 1143 (35·7 per cent) were smokers and 119 (3·7 per cent) had a former history of tobacco consumption (data missing from 47 patients) In all, 125 patients (3·9 per cent) were diabetic (114 diabetes mellitus type II and 11

Table 1 Preoperative study data

Patient history
  Sex
  Age
  Consumption of alcohol (g ethyl alcohol per day)
  Consumption of nicotin (no. of packs per year)
  Diabetes mellitus (type I, type II, impaired glucose tolerance)
  Symptoms of cardiovascular disease (dyspnoea, angina pectoris, intermittent claudication, myocardial infarction)
  Symptoms of respiratory disease (cough, sputum, haemoptysis, etc.)
  Symptoms of gastrointestinal disease (constipation, diarrhoea, vomiting, haematemesis)
  Symptoms of urological disease (nycturia, dysuria)
  Complications following previous surgery
Physical examination
  Body weight : height ratio
  Lung and heart examination (auscultation, percussion)
  Neck vein congestion
  Abdominal examination (i.e. liver and spleen)
Technical examinations
  Radiography of the chest*
  Electrocardiography*
  Lung function tests*† (vital capacity, forced expiratory volume in 1 s)
  Haematology (haemoglobin, haematocrit, white cell count)
  Blood chemistry (potassium, serum glutamic–oxaloacetic transaminase, creatinine, quick test)
ASA classification‡
Operative details
  Group of planned operative procedure (*Table 3*)
  Assumed malignancy of the disease (including the result of preoperative histopathological examinations)

*Not routinely performed in patients aged under 45 years and undergoing minor operation, excluding entry to the abdominal or thoracic cavity. †Low number of registered cases did not allow statistical analysis. ‡American Society of Anesthesiologists (ASA) grade was not recorded routinely during the first year of the study

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Paper accepted 4 March 1996

Table 2 Postoperative systemic complications

Complication	No. of patients
Pneumonia	77 (23·9)
Atelectasis	48 (14·9)
Cardiac events	46 (14·3)
Septic complications	36 (11·2)
Thromboembolism	12 (3·7)
Other*	103 (32·0)
Total	322† (100)

Values in parentheses are percentages *Includes urogenital infection; †15 missing values

Table 3 Postoperative study data

Operative procedure*	No. of patients	No of systemic complications
Group 1	1317	55 (4·2)
Group 2	1194	146 (12·2)
Group 3	459	76 (16·6)
Group 4	256	60 (23·4)
Total†	3226	337 (10·4)

Values in parentheses are percentages. *Group 1, operations excluding entry to the abdominal or thoracic cavity; group 2, minor abdominal interventions (including minimal invasive surgery); group 3, thoracic surgery; group 4, major upper abdominal surgery and retroperitoneal interventions. †Data missing from 24 patients

Table 4 Results of univariate analysis for risk of general complications

Variable*	χ^2	d.f.	P
Age	38·24	4	< 0·00001
Symptoms of respiratory disease	38·49	1	< 0·00001
Abnormal lung auscultation	30·65	1	< 0·00001
Abnormal chest radiograph	26·04	1	< 0·00001
Low haematocrit (men < 40 per cent, women < 37 per cent)	30·55	1	< 0·00001
Increasing ASA grade	97·09	3	< 0·00001
Severity of operative procedure (groups 1–4)	129·21	6	< 0·00001
Malignant disease	69·31	1	< 0·00001
Cigarette consumption (packs per year)	22·81	3	0·00004
Alcohol consumption (> 20 g per day)	19·87	2	0·00005
Serum glutamic–oxaloacetic transaminase (> 60 units l^{-1})	15·61	1	0·00008
Quick test (< 0·70)	15·57	1	0·00008
Pathological lung percussion	14·37	1	0·00015
Leucocyte count (> 9·6 × 10^6)	16·78	2	0·00023
Symptoms of gastrointestinal disease	29·13	8	0·00030
Neck vein congestion	16·17	2	0·00031

*Variables with a P value of < 0·001 in χ^2 analysis. ASA, American Society of Anesthesiologists

diabetes mellitus type I) (data missing from 17 patients). Ninety patients (2·8 per cent) had a history of myocardial infarction (data missing from five patients) and 508 (19·9 per cent) of 2554 patients had symptoms of respiratory disease (chronic bronchitis, asthma bronchiale). Mean(s.d.) excess weight was 7·7(12) kg for men and 11·0(13·2) kg for women, based on ideal body-weight (body length (cm) − 100) − ((body length (cm) − 100) × 10 per cent (men) or × 15 per cent (women)).

Cardiopulmonary examination revealed arrhythmias in 118 of 3239 patients (especially atrial fibrillation and supraventricular premature beats); 355 of 3245 had pathological heart sounds; and 286 of 2570 patients had abnormal lung sounds. Some 2236 patients underwent preoperative chest radiography, with a pathological finding in 651 cases (29·1 per cent); 2655 underwent electrocardiography, which was abnormal in 514 cases (19·4 per cent).

With regard to the new classification of physical status of the American Society of Anesthesiologists (ASA)[10], before operation 43·1 per cent (1088 of 2524 patients) were classified as ASA grade I, 41·4 per cent (1046) as ASA grade II, 13·7 per cent (345) as ASA grade III, 1·8 per cent (45) as ASA grade IV and none as ASA grade V.

Planned procedures were divided in four groups, each of which included operations of comparable status (data missing from 24 patients): group 1, operations excluding entry to the abdominal or thoracic cavity; group 2, minor abdominal interventions (including minimally invasive procedures); group 3, thoracic surgery; group 4, major upper abdominal surgery and retroperitoneal interventions.

Statistical analysis

All information was stored in a computer database. Each preoperative variable (*Table 1*) was correlated first with systemic postoperative complications by univariate χ^2 analysis. Factors with a highly significant result in univariate analysis ($P < 0·00001$) were then subjected to stepwise logistic regression analysis with the standard program of the Statistical Package for the Social Sciences (1990, version 4.0) (SPSS, Chicago, Illinois, USA).

Results

Systemic complications are shown in *Table 3* and occurred in 10·4 per cent (337 patients) during the postoperative course. Some 42 patients died during the hospital stay (1·3 per cent); 23 were operated on for malignant disease: 14 as a palliative procedure and nine with curative intent.

By univariate analysis, the following parameters had a highly significant ($P < 0·00001$) association with postoperative systemic complications: age, respiratory symptoms, abnormal lung sounds, pathological chest radiograph, low haematocrit (less than 40 per cent for men and less than 37 per cent for women), increasing ASA grade, severity of operative procedure (groups 1–4; *Table 3*) and finally malignant *versus* benign disease (*Table 4*). These parameters were analysed separately by stepwise logistic regression analysis. Finally, only four variables had a significant association with systemic postoperative complications with decreasing significance: severity of operative procedure, increasing ASA grade, symptoms of respiratory disease and malignancy.

Based on these findings a multifactorial risk scoring system was created (*Table 5*). The four groups of operative procedure are represented by a maximum of 4 points as well as the four ASA grades. Respiratory symptoms and malignant character of the disease are each counted as 1 point. Thus a patient with ASA grade I (1

Table 5 Results of multiple logistic regression analysis: risk scoring system

Variable*	Correlation coefficient (*r*)	*P*	Risk score (range of points)
Group of operative procedure (1–4)†	0·1667	<0·00001	1–4
ASA classification (I–IV)‡	0·1066	<0·00001	1–4
Respiratory symptoms (no = 0 points, yes = 1 point)	0·0693	0·002	0–1
Pathology of the disease (benign = 0 points, malignant = 1 point)	0·0541	0·0101	0–1
Minimum possible			2
Maximum possible			10

*Analysis of variables with a P value of $<0·00001$ in χ^2 analysis. †Group 1, operations excluding entry to the abdominal or thoracic cavity; group 2, minor abdominal interventions (including minimal invasive surgery); group 3, thoracic surgery; group 4, major upper abdominal surgery and retroperitoneal interventions. ‡Patients with American Society of Anesthesiologists (ASA) grade V are unable to undergo elective surgery

Table 6 Retrospective application of the risk scoring system in comparison with the American Society of Anesthesiologists classification*

Score	No. of patients	Systemic complications
Risk class†		
A	1532	76 (5·0)
B	853	153 (17·9)
C	102	34 (33·3)
Total‡	2487	263 (10·6)
ASA grade		
I	1087	57 (5·2)
II	1046	121 (11·6)
III	343	77 (22·4)
IV	45	12 (26·7)
Total	2521	267 (10·6)

Values in parentheses are percentages. *Includes data from 1989 to 1992 (American Society of Anesthesiologists (ASA) classification not routinely registered in 1988). †Risk class A, up to 5 points; B, 5–7 points; C, 8–10 points. ‡Thirty-four missing values

point), without symptoms of respiratory disease (0 points), undergoing haemorrhoidectomy (1 point) for benign disease (0 points) would be classified with a minimum of 2 points, whereas a patient with chronic bronchitis (1 point) in ASA grade IV (4 points), undergoing oesophagectomy (4 points) for cancer (1 point) is classified with a maximum of 10 points.

Some 2487 valid patient data (an additional 34 missing values) could be scored retrospectively with this new system, as ASA grade was not collected in 1988, the first year of the study. Patients with a total maximum of 4 points could be classified as a low-risk group with a systemic complication rate of 5·0 per cent (76 of 1532 patients); 5–7 points represented an intermediate risk group with 17·9 per cent having systemic complications (in 153 of 853 patients); and those with more than 7 points had a high risk of 33·3 per cent (34 of 102) of developing systemic postoperative complications. According to these risk groups, three risk classes can be defined: class A, patients at low risk with a maximum of 4 points; class B, patients at intermediate risk with 5–7 points; and class C, patients at high risk with 8–10 points.

The rate and frequency of systemic complications in the various ASA grades were also examined: ASA grade I, 5·2 per cent (57 of 1087 patients) of systemic complications; ASA II, 11·6 per cent (121 of 1046); ASA III, 22·4 per cent (77 of 343); ASA IV, 12 of 45 patients (*Table 6*).

Discussion

One of the main preconditions for eliminating mortality from elective surgery consists of a systematic prospective analysis of patient data large enough to perform multivariate analysis of possible risk factors associated with life-threatening complications and leading to a fatal outcome.

In the present study four significant risk factors for systemic perioperative complications after elective general surgery could be identified. It is well known that the operative procedure *per se* is one of the most important factors influencing the postoperative outcome[2,6]. The ASA classification and the symptoms of respiratory disease focus on the patient and the systemic disease[6,10,11]. The presence of pulmonary disease becomes even more important in the case of emergency procedures for gastrointestinal perforation[12]. Previous reports have shown that simple clinical information provides as much data about the patient's risk of developing postoperative pneumonia as lung function tests[7]. Finally, the disease is measured by its benign or malignant character. Several studies of risk assessment have shown the value of including histological information in scoring systems[13,14].

In the past, several scoring systems have been suggested to estimate individual operative risk[4,8,13,15]. Only a few focus on systemic perioperative and postoperative complications without any limitations[10,14]. The ASA classification is the only system that is readily usable at the bedside. This scoring system has the disadvantage that only patient-related data are considered. This paper suggests a risk scoring system based on the four above-mentioned variables: severity of operative procedure, ASA classification, respiratory symptoms and disease pathology. These variables include patient data as well as data describing the planned operative procedure and the disease itself. In order to avoid complicating the scoring system, the different values of the correlation coefficients were not taken fully into account (*Table 5*). The operation and ASA classification have been weighted equally, despite a moderate difference in the correlation coefficient of 0·0601. Nevertheless, we are able to define a high-risk group of patients with more general complications (+24·7 per cent) than in ASA grade IV. At the same time, this new high-risk group includes an increased (+127·8 per cent) number of patients, compared with ASA grade IV.

The results of this analysis indicate that the risk of elective general surgery can readily be predicted using the proposed risk scoring system. Patients at high risk of perioperative and postoperative systemic complications are more likely to be defined than with the ASA classification alone.

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British Journal of Surgery 1996, 83, 1792

Short note

Chemical composition and potential hazards of electrocautery smoke

P. M. SAGAR, A. MEAGHER, S. SOBCZAK* and B. G. WOLFF

*Division of Colon and Rectal Surgery and *Section of Occupational Safety, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA*

Correspondence to: Dr B G. Wolff, Division of Colon and Rectal Surgery, East 6A, Mayo Clinic, 200 1st St SW, Rochester, Minnesota 55 905, USA

Electrocautery is widely used for dissection of tissues and cauterization of blood vessels. A visible plume of smoke is produced, which has an unpleasant odour and can induce acute and chronic inflammatory changes in the respiratory tract[1]. Airborne particles are not effectively filtered or evacuated by operating room scavenging systems and facial masks only offer protection from large particles. Little is known about the chemical composition of this smoke and the health risks to the operating room staff have not been identified.

The aim of this study was to determine the chemical composition of electrocautery smoke produced in the course of standard colorectal surgery.

Patients and methods

Six patients (three men) were studied during the course of small bowel resection ($n = 2$), hemicolectomy, proctocolectomy, adhesiolysis and the York–Mason procedure Multiple samples of the smoke plume generated by the use of electrocautery were collected by means of a small calibre (6 35 mm diameter) plastic tube taped near to the end of the electrocautery pencil or held in the plume above the pencil. The opening of the tube was close to, but not in contact with the Teflon (Du Pont, Wilmington, Delaware, USA) tip of the pencil The tubing led out of the operating field and into collecting media (charcoal, silica gel and Tenax, Chrompac, Raritan, New Jersey, USA). The flow rates used to collect the analysate were chosen according to National Institute for Occupational Health and Safety guidelines[2] The constituents of the collected smoke were determined by high-performance liquid chromatography, gas chromatography with a thermal energy analyser, ion chromatography and mass spectrometry. Specifically, smoke samples were tested for polycyclic aromatic hydrocarbons, nitrosamines, nitrates, nitrites and volatile organic compounds. The collection of smoke was continuous throughout each operation No attempt was made to record the duration of use of electrocautery during each procedure No other suction devices were employed while electrocautery was in use.

As there was a possibility that the collection samples may have become contaminated secondary to heat generated by the electrocautery pencil damaging the tubing, control samples were obtained from the tubing with the electrocautery tip intermittently switched on and placed on the surface of a small container of water (to establish an electrical circuit and heat the pencil).

Paper accepted 25 January 1996

Results

Electrocautery smoke was found to contain significant levels of benzene, ethyl benzene, styrene, carbon disulphide and toluene. Detectable quantities of at least one of these chemicals was found in each of the patients studied. No such chemicals were found in the control experiment. The maximum amount of each chemical detected is shown in *Table 1*. No nitrates, nitrites or nitrosamines were detected.

Table 1 Chemical composition of electrocautery smoke

	Maximum level detected (μg/m^3)
Benzene	71
Ethyl benzene	36
Styrene	21
Carbon disulphide	1·5
Toluene	460

Discussion

Previous studies of electrocautery during reduction mammoplasty have shown the smoke to be mutagenic but the authors were unable to identify the organic compounds involved[3,4]. Benzene, a known carcinogen, was identified in the current study in significant quantities. The recommended amount of exposure to benzene is nil. The detection of benzene in the smoke in the present study is therefore a matter of some concern. None of the other substances detected is a carcinogen but each is known to cause irritation to the eyes, dermatitis, central nervous system effects, and hepatic and renal toxicity.

It should be emphasized that this study did not attempt to give an estimate of the level of exposure of the surgeon or theatre staff in the course of these procedures but simply to identify the chemical composition of the smoke. Indeed, it would not be valid to extrapolate the concentrations of the constituents of the smoke in the vicinity of the electrocautery pencil to the concentration in the ambient air.

This was a small-scale pilot study of routine cases with minimal tissue destruction. It is not the purpose of this report to suggest restriction of the use of electrocautery (which the authors continue to use enthusiastically). Nevertheless, in view of the widespread use of electrocautery, further studies would appear to be needed to determine the extent of exposure of all operating room personnel and, if necessary, to develop methods to reduce risks to health.

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British Journal of Surgery 1996, 83, 1793–1794

Short note

Port-site metastases following diagnostic laparoscopy

E. J. M. NIEVEEN VAN DIJKUM,
L. Th. DE WIT, H. OBERTOP and
D. J. GOUMA

Department of Surgery, Academic Medical Centre, University of Amsterdam, The Netherlands

Correspondence to Dr E J M. Nieveen van Dijkum, Academic Medical Centre, G4-144, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

Diagnostic laparoscopy and laparoscopic ultrasonography is being used increasingly in the staging of gastrointestinal malignancy. Advantages of laparoscopic staging are change in tumour stage and prevention of unnecessary laparotomy[1,2]. Port-site metastases have been reported after up to 4 per cent of laparoscopic colonic resections and following laparoscopic cholecystectomy in patients with occult malignancy[3,4]. Patients having diagnostic laparoscopy are potentially at risk for port-site metastasis. The incidence of port-site metastasis was studied following diagnostic laparoscopy and ultrasonography for gastrointestinal malignancy

Patients, methods and results

Between June 1992 and July 1995, 250 patients underwent diagnostic laparoscopy for staging of gastrointestinal malignancy that was considered resectable after conventional staging All records were analysed retrospectively for tumour recurrence at the trocar insertion or port site. Methods of laparoscopic staging were as follows: three trocars were used and a maximum carbon dioxide pneumoperitoneum of 15 mmHg pressure After inspection the abdominal cavity was irrigated with 500 ml isotonic saline for cytological examination. Biopsies of suspected metastatic lesions were taken with biopsy forceps or large-bore biopsy needles. Biopsies were not performed in patients with potentially resectable tumours.

Only histologically proven metastasis and tumour ingrowth were used as exclusion criteria for further surgical exploration.

Some 250 patients were included for analysis with periampullary (121 patients), liver (24), proximal bile duct (26), oesophageal (66) and other intra-abdominal malignancy (13). Seven patients (2·8 per cent) were lost to follow-up

In four patients (1·6 per cent) port-site metastases developed during follow-up after diagnostic laparoscopy. Biopsies performed during laparoscopy confirmed metastasis in two of these patients (*Table 1*). The other two had no metastases seen during laparoscopy and biopsy was not performed During exploratory laparotomy in the latter two patients, however, locally advanced tumours were found which were confirmed on biopsy. Mean survival of patients, after detection of the port-site metastasis was 2 (range 1–3) months.

Paper accepted 23 February 1996

Discussion

Patients with port-site metastases had irresectable tumours shown during diagnostic laparoscopy or exploratory laparotomy and underwent palliative treatment. Progression of disease could be expected, but it was remarkable that the metastases developed at trocar sites and not in a laparotomy scar. A laparoscopy-related factor may be responsible for the development of port-site metastasis.

Direct tumour contact with the abdominal wall may be one cause. Tumour seeding through the puncture wound following percutaneous biopsy has been described[5]. The use of fine biopsy needles lowered the incidence compared with large needles, but seeding was not prevented completely.

The use of carbon dioxide pneumoperitoneum at a high intra-abdominal pressure may lead to circulation of floating tumour cells and local contact of these cells with the injured peritoneum. This might create a favourable condition for adherence of tumour cells. Animal experiments, however, did not support this mechanism[6].

The aetiology of port-site metastasis is unknown but it is an important long-term complication of diagnostic laparoscopy. The incidence was 1·6 per cent but occurred only in patients with advanced disease. Considering the incidence of port-site metastasis after laparoscopic colonic resection and laparoscopic cholecystectomy for occult gallbladder carcinoma, prevention seems to be indicated[3,4]. Biopsy of primary resectable tumours should be avoided, so that curative resection will not be jeopardized. Biopsies should be taken only of metastatic or obviously irresectable disease to prevent unnecessary laparotomy. Port-site metastasis will not adversely influence the limited survival of these patients. The mechanism of port-site metastasis requires further investigation to ensure that this complication does not jeopardize treatment of potentially curable tumours.

Table 1 Clinical findings in four patients with port-site metastases

Patient no.	Primary tumour	Cytology following peritoneal lavage	Positive biopsy during laparoscopy	Local or advanced disease*	Exploratory laparotomy	Time interval (months)†
1	Pancreatic head	Negative	—	Local	Bypass	10
2	Pancreatic head	Atypical	—	Local	Bypass	5
3	Stomach	Atypical	Liver and peritoneal metastases	Advanced	—	2
4	Liver	—	Liver metastases	Advanced	—	3

*Local disease, tumour ingrowth in surrounding structures; advanced disease, disseminated disease with distant metastases. †Time interval between laparoscopy and diagnosis of port-site metastasis

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Corrigendum

R. Farouk J. Edwards, M. Thorne, W. Young, A. W. MacDonald, J. R. T. Monson and P. W. R. Lee. Brush cytology for the diagnosis of rectal carcinoma. *British Journal of Surgery* 1996; **83**: 1456–1458.

The photograph appearing with the legend for *Fig. 1* was transposed with the photograph for the legend accompanying *Fig. 2*. This error arose because the figures submitted to the Journal had been incorrectly labelled.

British Journal of Surgery 1996, 83, 1795–1799

Correspondence

Laparoscopic inguinal hernia repair

Sir

We read the interesting Review by Messrs Liem and Vroonhoven on laparoscopic inguinal hernia repair (*Br J Surg* 1996; 83: 1197–204), and agree with the authors that it is premature to advocate a transition from conventional to laparoscopic techniques on a large scale We were surprised that no comment was made on the risk of mesh infection and pubic osteitis after laparoscopic herniorrhaphy. Several cases of such a complication have been reported[1–4]. In theory, infection should not be encountered after a laparoscopic approach for several reasons: the prosthesis introduced through the port has no contact with the skin, it is placed deep and the operation site is away from the port wound[3]. Laparoscopic experience shows that this is a definite risk and was reported in 0·1 to 0·5 per cent in large series[1,2]; this is close to the rate reported after conventional prosthetic repair. The mechanism of this complication is unclear; it could be an unrecognized injury of the bladder or the bowel, or even a postoperative haematoma secondarily infected. In the majority of patients the prosthesis had to be removed. As osteitis can be a tragedy for any patient, extra care must be taken when performing laparoscopic hernia repair and patients should be informed about this risk before operation.

K. Slim
D. Pezet
J. Chipponi

Department of General and Digestive Surgery
Hôtel-Dieu, BP 69
F-63 003 Clermont-Ferrand Cedex 1
France

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Sengstaken tube for bleeding rectal angiodysplasia

Letter 1

Sir

We read with interest the article by Mr Roy *et al* (*Br J Surg* 1996, 83: 1111). The authors describe this as a 'new method to control rectal bleeding', but we should like to point out that a similar technique has already been reported in a patient with rectal varices[1].

C. Maxwell-Armstrong
R. J. C. Steele

Department of Surgery
University Hospital
Queen's Medical Centre
Nottingham NG7 2UH
UK

1 Maxwell-Armstrong CA, Whittaker S, Pye G, Steele RJC, Hardcastle JD. Use of Sengstaken tube to control rectal variceal haemorrhage. Illustrated Case Reports. *Gastroenterology* 1995; 2· 1.

Letter 2

Sir

We were interested in the article by Mr Roy *et al.* This technique is similar to the use of a Foley catheter to treat delayed postoperative haemorrhage following haemorrhoidectomy[1,2]. An important element of such treatment, however, is that the distal end of the catheter should be fixed to the buttock under gentle tension, as in the use of a Sengstaken oesophageal balloon. In both instances the main effect is due to traction applied to the tube which forces the balloon to compress the adjacent vessels. In oesophageal varices, for example, inflating the oesophageal balloon contributes little, if anything, to stopping the haemorrhage[3].

L. Basso
I. Ahmed

Royal College of Surgeons in Ireland
Department of Surgery
Navan
County Meath
Ireland

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Preliminary experience with butyl-2-cyanoacrylate adhesive in tension-free inguinal hernia repair

Sir

I read with interest the article by Mr Farouk and colleagues (*Br J Surg* 1996; 83. 1100) on the use of glue in inguinal hernia repair, and look forward to a report on their prospective randomized trial. They are mistaken in saying that the use of tissue adhesive for tension-free mesh repair has not previously been reported. Canonico *et al.*[1] in 1995 compared two consecutive groups of patients undergoing Lichtenstein mesh repair: one group of 100 patients had human fibrin glue under and upon the Marlex (C R. Bard, Massachusetts, USA) mesh, the second group of 98 patients did not. They concluded that there were no significant differences in the number of seromas observed, but the group that had glue to secure the mesh had a lower number of postoperative haematomas (this achieved statistical significance)

C. M. Cheek

Royal College of Surgeons of England
35–43 Lincoln's Inn Fields
London WC2A 3PN
UK

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Pulmonary function after laparoscopic cholecystectomy in the elderly

Sir

We read with interest the paper by Dr Milheiro and colleagues (*Br J Surg* 1996; 83: 1059–61) on postoperative pulmonary function following laparoscopic cholecystectomy in 50 patients, 20 of whom were older than 69 years of age. We find it difficult to understand, however, how their elderly cohort of patients had such impressive preservation of pulmonary function, 90 per cent of preoperative values of static lung volumes and 87 per cent of forced expiratory flow at 24 h after surgery. We have also gathered prospectively pulmonary function data on 100 patients undergoing laparoscopic cholecystectomy and cannot find any correlation between recovery of pulmonary function and age (*Table 1*).

Table 1 Age and postoperative pulmonary function

Age group	<60	60–69	>69	P†
No. of patients	65	26	6	
FVC (24 h)*	76 (61–89)	70 (60–91)	72 (53–91)	n.s.
FEV_1 (24 h)*	72 (59–89)	70 (56–85)	70 (59–87)	n.s.
PEFR (24 h)*	70 (56–90)	68 (55–87)	69 (59–115)	n.s.
Postop. stay (days)*	1·0 (1·0–2·0)	2·0 (1·0–2·2)	2·0 (2·0–3·5)	0·005

*Values are median (interquartile range) and represent the percentage of preoperative forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and peak expiratory flow rate (PEFR). n.s., not significant. †Mann–Whitney *U* test

You will note that our patients' postoperative pulmonary function is almost identical to that obtained by Milheiro *et al.* for the younger age group of less than 70 years old, suggesting that any differences between studies cannot be explained by differences in anaesthetic or operative technique.

We agree with the conclusions of Dr Milheiro and colleagues regarding the excellent results of laparoscopic cholecystectomy in the elderly population. The postoperative hospital stay for our elderly patients was only 2 days which compared favourably with the 1 day required for patients under 60 years of age.

D. H. Wallace
P. J. O'Dwyer

Department of Surgery
Western Infirmary
Glasgow G11 6NT
UK

Prospective study of the aetiology of infusion phlebitis and line failure during peripheral parenteral nutrition

Sir

It is established that development of infusion thrombophlebitis is influenced by the infusate, the catheter through which it is delivered, the vein chosen, and the duration of infusion[1]. The precise interplay of these factors remains uncertain and the paper by May *et al.* (*Br J Surg* 1996; 83: 1091–4) is a welcome addition to the debate regarding the aetiology of the condition. Their methodology however is open to criticism. A standard feed was used, but infusion rate was dependent on the patient's weight and this may have influenced the development of phlebitis[2]. The authors suggested that the risk of thrombophlebitis was influenced by catheter length. If valid conclusions regarding catheter properties are to be made, like must be compared with like. In group 3 the infusion devices used differed not only in length, but also in material and tip profile, both of which may influence the development of phlebitis. Furthermore, the longer catheter was inserted over a guidewire, which itself may have influenced subsequent morbidity. It was incorrectly stated that, in a previous study[3], 18-G 15-cm catheters were associated with a higher incidence of thrombophlebitis. Rather, 22-G polyurethane and 23-G silicone rubber catheters were compared and the risks of thrombophlebitis were similar. Occlusion, or failure of a volumetric pump to maintain infusion in the absence of signs of thrombophlebitis, was more common in the narrower catheters, and was caused by feed inspissation within the catheter lumen. May *et al.* suggest that occlusion was due to venous thrombosis in their study, yet give no evidence that it was the vein, rather than catheter lumen that was occluded. If occlusive episodes are excluded from group 4, the morbidity is substantially reduced. As the authors state, grading of thrombophlebitis is imprecise and phlebitis may rapidly progress in severity[4]. In their arbitrary scoring system, the weight given to severe phlebitis may account for the significant difference observed between groups. The frequency of cannula or catheter review was not stated. During cyclical infusion, review may have been more frequent, and therefore phlebitis would be expected to be more severe during continuous infusion. Comparison of phlebitis severity is of little value; it is only necessary to record that the complication occurs. The time to its development is paramount, and actuarial analysis should be used because data are likely to be censored[5].

N. J. Everitt

Department of Surgery
Doncaster Royal Infirmary
Armthorpe Road
Doncaster DN2 5LT
UK

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Authors' reply

Sir

In reply to Mr Everitt's concern about frequency of cannula and catheter review, I am able to confirm that review of the patient's IV access site was carried out twice daily by the nutrition nurse specialist or, in her absence, by a member of the research team. This was in addition to the inspections by the ward nursing staff as per the protocol for patients with peripheral IV access devices *in situ*.

The authors would like to thank Mr Everitt for his comments and interest in this paper. Notwithstanding his comments, the conclusions are that mechanical trauma does play an important part in the development of infusion phlebitis during PPN. The duration of infusion, catheter length and surface area are significant factors in phlebitis development. These conclusions remain valid.

D. Palmer
J. MacFie

Department of Surgery
Scarborough Hospital
Scarborough YO12 6QL
UK

Stapling instruments for intestinal anastomosis in colorectal surgery

Sir

To write a review is always a considerable and difficult task. Mr. Moran clearly fulfilled all expectations with his excellent article

(*Br J Surg* 1996, 83: 902–9). I apologize for correcting a small, but from our viewpoint, significant error.

The author cited correctly Humér Hultl, a Hungarian surgeon (reference 5), who 'produced the first sophisticated stapling instrument in Budapest in 1908'. Unfortunately, under references 6 and 7 he cited the name of the Hungarian surgeon Aladár Petz as 'von Petz'. Although not stated, this form of Aladár Petz's name implies that he was German or Austrian. Aladár Petz was Hungarian and the leader of the surgical department of the hospital in the city Gyor. This hospital is now named Petz Aladár megyei Kórház, Aladár Petz County Hospital. His modification of Humer Hultl's heavy and difficult stapling instrument made the instrument 'the most renowned'. In some places it is still being used. I used Petz's machine in a few patients needing partial gastrectomy until my retirement in 1992. The Zentralblatt fur Chirurgie always published the name of the author of the article with the preposition 'von', which means from or by[1] Aladár Petz was not a noble German, but an excellent and renowned Hungarian surgeon, a person of high dignity, who evidently deserves this modest comment.

We, as other small nations, have given significant and unique scientific contributions to mankind, for example from Ignacz Semmelweisz to Ede Teller. I do hope, on the basis of my comments I shall be considered *only* as a patriot and not as a nationalist[2].

M. Gergely

Szolnok-Szóröpuszta
5002 POB 8433
Hungary

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A better bridge for loop stomas

Sir

We read with interest the various modifications suggested on this subject, described recently in the journal. Messrs Richardson and Leicester (*Br J Surg* 1996; 83: 1011) describe a technique whereby a 16-Ch nasogastric tube is passed under the loop of colon and joined together above the bowel with a single nylon suture. If the bridge is not fixed to any part of the abdominal wall, how can it support the stoma and prevent it from receding? In case the mucocutaneous stitches (between the stoma and abdominal wall) cut through, is it not more likely for the 'bridge' to retract along with the stoma rather than to prevent it from doing so?

Messrs Habib and Williams describe the alternative of a double throw of a nylon suture as a bridge (*Br J Surg* 1996; 83: 1161). This again has the theoretical danger of acting as a bowstring across the loop of bowel and causing damage to it, especially when there is tension on the stoma.

We entirely agree that a Foley catheter or nasogastric tube is probably softer and less traumatic than a proprietary bridge. If the ends of such devices are tunnelled subcutaneously and brought out on to skin 6–8 cm from the edges of the stoma, it will be convenient to attach the stoma bag close to the edges of the stoma and prevent leakage of any effluent on to the parastomal skin. In addition there is no undue protuberance of the stoma where the colostomy is large.

S. Sudhindran
K. J. Regunath

Department of Surgery
Leighton Hospital
Crewe CW1 4QJ
UK

Simultaneous aortorenal homograft transplantation: expanding the indications for renal and vascular replacement

Sir

I read with some concern the paper by Messrs Mestres, Talbot-Wright and Carretero (*Br J Surg* 1996; 83· 918) I feel its title is inappropriate. The authors report a single case in which they have transplanted an allograft human aorta and iliac system to replace the calcified and partly-aneurysmal infrarenal aorta and common iliac arteries of a recipient of a live donor renal transplant.

We were forced to give up human allograft arterial grafts in the early 1960s as they became universally aneurysmal, and there is no objective evidence that co-existent immunosuppression will alter this unfortunate natural history. This paper is being published when the patient has been followed for only 1 year, and I believe its publication is therefore premature. Moreover, the claim that the operation expands the indications for renal and vascular replacement is unduly optimistic.

I see no reason why this patient's aorta should not have been replaced with a conventional Dacron (Du Pont, Stevenage, UK) graft into which the renal artery could undoubtedly have been implanted or, alternatively, an end-to-end anastomosis of the renal artery to an endarterectomized internal iliac artery could have been fashioned distal to the graft if the iliac aneurysm warranted resection.

C. W. Jamieson

Department of Surgery
St Thomas' Hospital
London SE1 7EH
UK

Diagnostic role of cytology in screen-detected breast cancer

Sir

We read with interest the paper by Dr Yiangou and colleagues (*Br J Surg* 1996; 83: 816–19) and feel we must respond The false-negative rate at this particular centre is unacceptably high[1]. Was any attempt made to repeat the C2 aspirates in view of the fact that there was radiological and/or clinical suspicion of malignancy? The fact that the cytopathologist achieved high positive predictive values for the C4 and C5 results suggests that the material reported as C2 must have been cytologically negative, and therefore the problem lies with the sampling technique.

Three reasons for false-negative results are listed, but no attempt has been made to determine how many of the C2 cases fall into each of the three categories. The fact that the stereotactic aspirates had fewer false-negative results confirms that accurate sampling of palpable lesions is probably not being achieved. We would like to know the histological type of the *in situ* ductal carcinomas, as comedo-type (high grade) ductal carcinoma *in situ* is much more easily diagnosed on cytology than are the intermediate and low-grade types Not all carcinomas have radiological and clinical features of malignancy, and it is important to know whether any of the women who had C2 diagnoses with benign radiological and clinical features subsequently developed malignancy.

The implication in this article is that the cytological diagnosis may be inaccurate, and this view can only be changed by providing the reader with the results of an impartial review of the false-negative cytology cases. Cytology is now a well established diagnostic technique in the right hands, well accepted by patients, and able to provide much more than a benign or malignant report[2,3]. It is essential that this ability to produce a rapid, accurate, preoperative diagnosis is fostered and developed. In response to the statement that cytological grading systems are not in wide use, we would emphasize that cytopathologists strive to provide the type of information that the surgeon requires for patient management. If the preoperative typing and grading of breast carcinomas are more widely requested they will soon become an integral part of all cytology reports, as they are relatively easy and quick to perform. Surely more information is better than less?

G. McKee
M. Kissin

Breast Unit
Royal Surrey County Hospital
Egerton Road
Guildford GU2 5XX
UK

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Prognostic significance of radial margins of clearance in rectal cancer

Sir

I read with interest the excellent paper written by Dr De Haas-Kock and co-workers (*Br J Surg* 1996; **83**: 781–5). As the authors point out correctly in their introduction, most of the predictive factors for local failure, such as T and N stage, Dukes classification and histological type and grade, are tumour-dependent factors, whereas only a few are surgeon- or surgery-dependent factors[1,2].

The intriguing point in this paper is that it is difficult to understand whether an involvement of radial resection margins (RRMs) has to be considered (1) a tumour-dependent factor, i.e. a biological indicator of tumour aggressiveness that clinicians cannot interfere with or (2) a simple marker of inadequate local excision, which could be appropriately corrected by extending the resection by some millimetres or centimetres, depending on the conditions in each particular case.

My main perplexity regards one point: the choice of a distance less or greater than 1 mm as the cut-off point for considering an RRM positive or negative. In fact, the choice of 1 mm as the cut-off point may mean that some of the nine recurrences in the 31 patients with positive RRMs are actually due to an inadequate local excision. I am not surprised that by maintaining this cut-off point, Ng *et al.*[3] and Adam *et al.*[4] reported percentages of local failures of 53 and 78 per cent respectively in positive cases, which is only to be expected when the surgical excision of cancer is incomplete.

In this context, the paper by Cawthorn *et al.*[5] in 1990, which simply considered the mesorectal spread as slight or extensive (depending on whether it was less or more than 4 mm) and reported its impact on survival and not on local recurrence, seems to suggest that involvement of the mesorectum indicates the poor prognosis of the patients more than it does the need to further extend the scope of the resection. The recent paper by Joyce *et al.*[6] which reported a substantial rate of local recurrence despite total mesorectal excision is in keeping with this interpretation.

Table 1 Prevalence and extent of mesorectal spread

Reference	No. of patients	Percentage with MS	Length of MS (cm)
Heald *et al.*[7]	113	4·4	2·0 (1·5–4·0)*
Quirke *et al.*[8]	52	27·0	1·4 (0·6–2·8)*
Cawthorn *et al.*[5]	167	70·0	0·4 (0·1–3·0)*
Scott *et al.*[9]	20	20·0	2·0 (1·0–3·0)*
Ist. Naz. Tumori[10]	50	40·0	>0·4 in 55%

*Values are median (range). MS, mesorectal spread

In conclusion, to clarify this matter surgeons should be acquainted with the prevalence and extent of mesorectal spread (*Table 1*). These data would also indicate the volume of resection necessary to have 'safe' margins of clearance. If the transection line falls in tumoral tissue (or within <1 mm of it), it is obvious that there will be an unacceptable recurrence rate. This fact does not imply, in contrast with the opinion of others[7–9], that in rectal cancer the mesorectum should always be removed *in toto*, but the involved part should certainly be removed.

F. Bozzetti

Department of Surgical Oncology
Istituto Nazionale per lo Studio e la Cura dei Tumori
Via Venezian, 1
20133 Milan
Italy

1 Phillips RKS, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Local recurrence following 'curative' surgery for large bowel cancer: II. The rectum and rectosigmoid. *Br J Surg* 1984; **71**: 17–20.
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Conservative management of fibroadenoma of the breast

Sir

Miss Alle and her colleagues from California (*Br J Surg* 1996; **83**: 992–3) indicate that recent trials of conservative management have found that most women wish to have their lump excised.

This statement is incorrect. The most recent study published in the *British Journal of Surgery* demonstrated that over 90 per cent of patients were happy with the conservative approach[1], supporting an earlier study from Oxford[2]. Our detailed study of the natural history of fibroadenoma has shown that few increase in size and that approximately one-third get smaller or disappear within 2 years of diagnosis[1]. This study also demonstrated that conservative management is safe, at least in younger patients.

I was surprised at the scant attention given to the use of ultrasonography as a diagnostic technique for fibroadenomas. As the authors point out, a combination of cytological diagnosis and clinical examination is not infallible, and a third diagnostic technique is necessary to try and limit the number of malignant lesions that are misdiagnosed. Ultrasonography is of value in follow-up The regimen outlined previously[1] was that all patients should have a single follow-up scan at 6 months to ensure that the lesion has not changed in size or that the characteristics of the lesion have not changed.

I note that there was no reference to support the statement 'excision has the attractions of minimal morbidity .'. A follow-up study of patients undergoing breast biopsy for lesions subsequently shown to be benign demonstrated that breast biopsy is not a procedure with minimal morbidity and should only be performed when there is a clear indication[3].

J. M. Dixon

Department of Surgery
Royal Infirmary
Edinburgh EH3 9YW
UK

1 Dixon JM, Dobie V, Lamb J *et al.* Assessment of the acceptability of conservative management of fibroadenoma of the breast. *Br J Surg* 1996, 83: 264–5
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Author's reply

Sir

Many thanks to Mr Dixon for his comments on this controversial subject. He contends that most women are happy with a conservative approach and his recent study supports this hypothesis[1]. His initial data from Oxford however, and studies from other centres suggest that the majority of patients with a palpable fibroadenoma would prefer to have it removed[2–4].

Ultrasonography is unlikely to improve the false-negative rate for cancer, which is negligible, but may improve the accuracy of the benign diagnosis and be of value in follow-up. For lumps that disappear, conservative management was obviously the correct approach. Unfortunately, these patients cannot presently be identified prospectively and two-thirds of patients will still have an 'undiagnosed' breast lump after 2 years. There are significant implications in leaving a lump in the breast without regular assessment and it is unrealistic to expect a young patient to return indefinitely. Therapeutic excision of a circumscribed benign breast lump should be associated with minimal morbidity[3]. Diagnostic biopsy following mammographic localization of an impalpable screen-detected lesion, which turns out to be benign, is a different surgical procedure[5].

As Mr Dixon comments, conservative management of fibroadenoma is safe, at least for younger patients in the short term. The issue for debate, however, is not whether this approach is safe but whether it is optimal.

K. Alle

Cancer Biology Division
Garvan Institute of Medical Research
St Vincent's Hospital
Sydney
New South Wales 2010
Australia

1 Dixon JM, Dobie V, Lamb J *et al.* Assessment of the acceptability of conservative management of fibroadenoma of the breast. *Br J Surg* 1996; 83· 264–5.
2 Dixon JM, Clarke PJ, Crucioli V, Dehn TCB, Lee ECG, Greenall MJ. Reduction of the surgical excision rate in benign breast disease using fine needle aspiration cytology with immediate reporting *Br J Surg* 1987; 74: 1014–16.
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Use of a laparoscopic trocar for percutaneous introduction of drains into intra-abdominal abscesses

Sir

With reference to the recent article by Messrs Singh, Lamparelli and Foley (*Br J Surg* 1996; 83: 670), we agree that percutaneous drainage is very effective.

Instead of an expensive disposable laparoscopic trocar and cannula it is cheaper to use a thoracic drain which is of greater diameter (a type of trocar catheter). Under local anaesthesia we perform a 10–12-mm incision and place the trocar and the silicon drain under ultrasonographic guidance into the intra-abdominal abscess.

The advantage of this technique is that the drain reaches a diameter of 24, 28 or even 32 Fr if necessary, promoting improved drainage of the cavity Rinsing or using light suction on the drain is also possible. A large enough skin incision avoids any need for dilatation before placement of the drain. One may use computed tomography to measure exactly the introduction angle and the distance between abdominal wall and abscess, thereby allowing easier positioning of the drain.

In the past year we have successfully treated five patients with this method without any complication

N. Demartines
M. von Flue
F. Harder

Department of Surgery
University of Basel Medical School
Kantonsspital, 21 Spitalstrasse
CH-4031 Basel
Switzerland

Authors' reply

Sir

Thank you for the opportunity of reply. Since submission of the paper we have had occasion to employ a non-disposable laparoscopic trocar for percutaneous drain introduction which has resulted in a reduction in the cost of the procedure For smaller abscesses we still prefer to use a disposable trocar as it is sharper and easier to control. Its retractable shield perhaps increases its safety during use

K. Singh
M. Lamparelli
R. J. E. Foley

Department of Surgery
Bedford Hospital
Bedford MK42 9DJ
UK

British Journal of Surgery 1996, 83, 1800–1802

Book reviews

Anal Fistula. Surgical Evaluation and Management

R. K. S. Phillips and P. J. Lunniss (eds). 257 × 192 mm. Pp. 185. Illustrated. 1995. London: Chapman and Hall Medical. £45.

This text really has to be a must for any surgeon with an interest in coloproctology. As the book outlines, fistulas have been a challenge since time immemorial The rewards reaped by Felix, court barber and surgeon to King Louis XIV, are unlikely to be reaped by all, but none the less satisfactory understanding of the pathology and surgical management of fistulas remains the prerequisite to successful treatment. This book presents a well balanced appraisal of the pathology of fistula. The reader would not need to read far beyond this text to have an understanding that should sustain him during a career with an interest in this subject. Several experts have been recruited and they outline the rationale behind their individual approaches in the management of this sometimes complex condition. If there is any criticism, it might be that a reader embarking in this area afresh might have difficulty deciding which was the most appropriate management for an individual condition. In this respect the approach to the difficult fistula at the end of the book provides excellent guidance It would be hard to single out individual contributions for particular praise as this book is universally of a very high standard. The chapters on epidemiology and pathogenesis are particularly enlightening. The radiological chapters on endoanal ultrasonography and magnetic resonance imaging move the reader to the forefront of what is possible with modern imaging. The individual chapters have been written by surgeons of considerable experience in the management of complex anal fistulas, and this comes across in the commonsense approaches that are carefully described.

D. C. C. Bartolo

Royal Infirmary
Lauriston Place
Edinburgh EH3 9YW
UK

Breast Surgery

N. Bricout. 275 × 193 mm. Pp. 424. Illustrated. 1995. Heidelberg: Springer. DM 248.

Surgery on the breast has often been thought of as a poor relation among other general surgical specialties; it is only in recent years that there has been a true recognition that the skill and cosmetic result associated with breast operations are important. It is welcome to see a book that covers all aspects of surgery of the breast. This volume was first published in French in 1992 and has been updated and excellently translated into English by Dr David LeVay. *Breast Surgery* opens conventionally with chapters on embryology and anatomy, and includes attractive vignettes to remind us why the author feels that morphological description is important in surgical practice. The following sections on operations for benign and malignant disease do occasionally read as if they have been included for completeness, before Professor Bricout moves on to the main subject of the book. This is essentially a textbook on plastic surgical procedures and in this area it really comes into its own. Some of the techniques are associated more with continental Europe than with the UK, but they are well described and illustrated. The author's attention to photographic detail is reinforced by an early chapter which gives guidelines on photography of the breast. Throughout this work the quality of the line drawings and illustrations is first rate, and the legends are clear. This is a well produced book which would certainly be a useful addition to any library. It will be well received by breast surgeons, particularly those who do not work closely with a colleague who specializes in plastic surgery.

M. J. Cooper

Royal Devon and Exeter Hospital
Barrack Road
Exeter EX2 5DW
UK

Color Atlas of Breast Diseases

R. E. Mansel and N. J. Bundred. 190 × 133 mm. Pp. 144. Illustrated. 1995. London: Mosby-Wolfe. £19.95.

This is a topical and original book; it is exhaustive of breast conditions and there are no major omissions. The plates are good, with clear and informative legends. It will be of interest to undergraduates, who may not be exposed clinically to all the conditions covered, and to junior surgical trainees. It will also be useful as a teaching aid to consultants My only adverse criticism is its attempt to combine an atlas with a mini textbook, and I feel the authors should have adhered more to the former. The text at the beginning of each chapter is necessarily superficial. This apart, I found this a very informative and attractive volume.

M. E. Lucarotti

Gloucestershire Royal Hospital
Great Western Road
Gloucester GL1 3NN
UK

Surgical Treatment of Aortic Dissection

H. G. Borst, M. K. Heinemann and C. D. Stone. 286 × 220 mm. Pp 357. Illustrated. 1996. Edinburgh: Churchill Livingstone. £90.

Dissection of the aorta is one of the most complex diseases of the cardiovascular system and one for which successful surgical treatment has remained elusive. Yet its incidence is two or three times that of ruptured abdominal aortic aneurysm, and its natural history is that up to 75 per cent of patients die within days and 90 per cent within weeks. Only in the past two decades have consistent results been reported, with surgery for acute proximal dissection carrying approximately a 15 per cent early mortality and a 60 per cent 10-year survival rate. To achieve such results presents a major challenge to the whole surgical team.

Surgical Treatment of Aortic Dissection is the first comprehensive text on the art and science of surgical treatment of the condition, and it is certainly for the connoisseur, for the 'surgeon-scholar'. Following brief sections on terminology, classification and history, there are chapters expounding incidence, aetiology, morphology and pathogenesis. Accounts of clinical presentation, diagnosis and assessment lead to the real meat of the book, namely the operative management of the various forms in which dissection presents. It is a truism that clinical conditions rarely present in the classical textbook form; it is also true that textbooks of surgery are often stronger on principle than on the details of technique. In this condition above most others, the surgeon must expect the unexpected and be prepared to improvise. The chapters on operative management not only present the principles and strategies essential to the management of operation for dissection, but also describe the variations seen in the operating theatre in a way which leads to rational decision-making and sound tactics, all of which are needed if the patient is to survive and have brain, spinal cord, kidneys and all other organs intact. The closing chapters on results, reoperation and follow-up emphasize the fact that most operations for dissection do *not* eliminate the pathology completely, but leave a highly abnormal aorta which may become the site of future problems. Thus, the operation is an incident in the overall care of the patient, for whom continuing expert surveillance is essential.

Borst's book is without equal in its completeness and clarity and is a fitting reminder of the immense contribution which he and his colleagues in Hanover have made in this field. It is for all those with an interest or involvement in dissection of the aorta; it is absolutely essential for any surgeon operating on patients with this condition.

J. D. Wisheart

Bristol Royal Infirmary
Marlborough Street
Bristol BS2 8HW
UK

Retroperitoneoscopy

A. Darzi (ed.). 282 × 221 mm. Pp. 152. Illustrated. 1996. Oxford: Isis Medical Media. £64.95.

This book is dedicated to the recently entered area of extraperitoneal laparoscopic surgery. Its purpose is to introduce videoendoscopy of the retroperitoneum and other areas, and to educate the reader about the application of this approach in general surgery (colonic mobilization, lumbar sympathectomy, groin hernia repair), vascular surgery (subfascial division of incompetent perforating calf veins, aortobifemoral bypass), urology (nephrectomy, ureteric surgery, bladder neck suspension), and plastic surgery (balloon-assisted augmentation mammoplasty). For each procedure there is a list of equipment required, a drawing showing the number, size and position of the ports required, and a diagram of the patient with suggested positions for monitors, surgeons, assistants and nurses. The line diagrams of operative procedures are outstanding and relate easily to the anatomy presenting to the surgeon at operation.

Both the editor and the authors are well suited to the task of constructing such a volume; they represent the leaders in their field. This multiauthored work is authoritative, comprehensive and represents a first attempt by laparoscopic surgeons to impart to their colleagues an understanding of the development of the technique, its applications and limitations, practical procedural details for its performance, preliminary clinical results, and an assessment of its future. However, development, interim results and technology are changing so rapidly that the book will not represent the current status for long. I have no doubt, however, that we will see further editions and, if so, I would like to find a discussion of alternative approaches and methods for some lesions. There is also a need for more information on the long-term results of this particular approach to be included in any future revision. The editor and the panel of experts covering different topics are to be congratulated for producing an excellent and useful book which, I am sure, will be popular with surgeons in training and experts in endoscopic surgery.

L. Fernández-Cruz

Hospital Clinic
Villaroel 170
08036 Barcelona
Spain

Atlas of Surgical Techniques

S. G. Economou and T. S. Economou. 310 × 235 mm. Pp 683. Illustrated. 1996. Philadelphia, Pennsylvania: W. B. Saunders. £129.

Any atlas of surgical techniques is hampered by the question of which surgical procedures to include, especially when the boundaries of general surgery are becoming increasingly blurred. This Atlas of 683 pages covers all aspects of general surgery but not in breadth. The section on vascular operations covers four procedures: carotid endarterectomy, abdominal aortic aneurysmectomy, aortofemoral bypass and femoropopliteal bypass. The chapter on the rectum covers but two procedures: abdominoperineal resection and repair of rectal prolapse. The American authors do not mention for whom the Atlas is intended. In the UK it would be of value to basic surgical trainees. In this respect it fills a gap in the market, in so much that the majority of atlases available in the UK are specialist in nature and not aimed at the trainee in general. The authors have succeeded in producing a worthwhile contribution which is well illustrated in black and white with a suitable text to match.

R. H. S. Lane

Royal Hampshire County Hospital
Winchester SO22 5DG
UK

Transplantation of the Liver

R. W. Busuttil and G. B. Klintmalm (eds). 285 × 220 mm. Pp. 903. Illustrated. 1996. Philadelphia, Pennsylvania: W. B. Saunders. £184.

This well written and well presented book fulfils an existing vacuum for an easy reference book on the various aspects of organ transplantation. The purpose of the volume, as is clearly laid out in the preface, is more than fulfilled by the editors who have brought together recognized international figures in their respective fields to contribute the various chapters The 13 sections and 85 chapters are well laid out and read easily from one to the next. Thomas Starzl's lucid chapter on the history of transplantation takes the reader through nearly 40 years of the development of organ transplantation to the situation that we know today. Some of the text tends to be slightly 'opinionated' but this simply reflects the practice of the individual authors. Although chapters such as that on ABO and human leucocyte antigen compatibility give a good and unbiased overview, recent developments, for instance in non-related living donor transplantation, are likely to outdate the contents quickly. All illustrations are appropriate and of high quality. Overall, this book is a must, not only for the specialist surgical trainee in liver transplantation but also for the practising transplant surgeon and for the whole range of clinical specialists involved in the care of the transplant patient.

K. K. Madavan

Royal Infirmary
Lauriston Place
Edinburgh EH3 9YW
UK

Atlas of General Surgery. 3rd ed.

D. C. Carter, R. C. G. Russell and H. A. Pitt (eds). 282 × 222 mm. Pp. 1185. Illustrated. 1996. London: Chapman and Hall. £95.

The volumes of Rob and Smith's *Operative Surgery* have served several generations of surgeons since their inception at the end of the second world war. They are usually to be found in the hospital library or (better I think) in the operating theatre office. The *Atlas of General Surgery* was conceived to meet the requirements of trainees and contains descriptions and illustrations of commonly performed operations selected from the entire series. The simple transposition from the main series ensures that the superb standard of description and illustration is maintained. The editors have selected wisely from the contents of the main volumes but there is inevitably some overlap (e.g. Cuschieri's description of laparoscopic cholecystectomy, and details of general laparoscopic techniques described by Siperstein). There are few descriptions of minimally invasive surgical techniques. There is no description of laparoscopic repair of groin hernias, Rutkow and Robbins stating simply that laparoscopic hernia repair has not been accepted by the American surgical profession. I could not find any description of thoracoscopic procedures. I was surprised that there was no description of total gastrectomy and no discussion of the merits of more extensive operations for gastric cancer. Notwithstanding three criticisms, this is a superb book which should be available to every general surgical trainee. I wonder, however, whether in 10 years' time even trainees will require a book that describes carotid endarterectomy, low anal anastomosis, parathyroidectomy, modified radical mastectomy and extensive resections for bile duct cancer

D. E. F. Tweedle

Withington Hospital
West Didsbury
Manchester M20 8LR
UK

Rob and Smith's Operative Surgery. Hepatobiliary and Pancreatic Surgery. 5th ed.

D. C. Carter, R. C. G. Russell, H. A. Pitt and H. Bismuth (eds). 282 × 222 mm. Pp. 674. Illustrated. 1996. London: Chapman and Hall. £155.

This is the fifth edition of *Hepatobiliary and Pancreatic Surgery* in the Rob and Smith *Operative Surgery* series. It provides a comprehensive description of the common and rarer procedures performed in modern hepatobiliary practice. Each section commences with a useful description of anatomy plus chapters on preoperative radiological investigation and patient preparation. There is a particularly excellent chapter on preoperative investigation and preparation of the patient with obstructive jaundice. As in any good volume on operative surgery, the text is kept to a minimum and the emphasis is on explanation and understanding of the procedures through line diagrams which, throughout the book, are of excellent quality. Each description of an operative procedure is usually prefaced by a short section on the history of the procedure, and also by a very useful section on principles and justification. These sections are appropriately brief and contain the necessary key references, no more than six or seven in each case. All procedures are described by well recognized authorities; there is a strong emphasis on each author's individual technique and this occasionally leads to a description of technique which would not be that used by the majority of biliary surgeons, e.g. the use of transhepatic stents in surgery for benign bile duct stricture. However, the vast majority of the operative descriptions are those of very well established and standardized techniques. This edition has also been very well edited in order to address the increasing role of percutaneous, endoscopic and laparoscopic diagnostic and therapeutic procedures in the management of hepatobiliary and pancreatic disease. In summary, this is an excellent operative surgical text. It will be particularly useful for trainees in hepatobiliary and general surgery but also as a reference text for practising hepatobiliary surgeons.

T. Diamond

Queen's University of Belfast
University Road
Belfast BT7 1NN
UK

Clinical Intensive Care

K. Hillman and G. Bishop. 229 × 153 mm. Pp. 835. Illustrated. 1996. Cambridge: Cambridge University Press. £35.

Intensive care is increasingly recognized as an area to which all acute specialty trainees should gain exposure. Those of us who run intensive care units (ICU) are faced with trainees of varying experience whose first question on the unit is 'What book should I buy?'. I think that I can now tell them – this one. The authors are well recognized and respected practitioners of intensive care in Australia, where ICU as a specialty has probably the best developed system. Their spur to write the book 'arose from the need to give resident staff rotating through our own ICU a crash course in intensive care medicine'. In this they have been successful. The opening chapters provide succinct and accurate guidance on the philosophy and organization of an effective ICU. The main chapters on core knowledge follow, and then more detailed discussion of specific conditions. The coverage is extensive, up to date, and at appropriate level for trainees. Each chapter has a short list of suggested further reading which is current and relevant. A coherent policy is evident throughout. Controversial areas are acknowledged and, where evidence for a technique or therapy is lacking, this is admitted. The general tone is of safe, effective clinical practice. Examples of troubleshooting guidelines are placed in tables throughout the text; these would have benefited from being allocated more space. I recommend this text strongly for trainees in ICU. It will also prove useful for those preparing to take a fellowship examination. It is also extremely good value.

D. W. McEwan

Royal Infirmary
Launston Place
Edinburgh EH3 9YW
UK

Progress in Surgery. Volume 22. Five Years of Laparoscopic Cholecystectomy: A Reappraisal

M. W. Büchler, E. Frei, Ch. Klaiber and L. Krähenbühl (eds). 245 × 174 mm. Pp. 216. Illustrated. 1996. Basel: Karger. Price not provided.

Laparoscopic cholecystectomy started to be performed in large numbers 6 years ago. Now is clearly an appropriate time for a reappraisal of this technique; unfortunately this book does not succeed in this task. The book is divided into four sections The first section consists of a historical review of both open and laparoscopic cholecystectomy, and chapters on the pathogenesis and investigation of gallstone disease. The second section discusses international experiences with the technique. Experiences from Chile, Hungary, Berlin, Austria, the UK and Switzerland are discussed, but unfortunately there is no chapter on experiences in the USA, the country that performs the greatest number of cholecystectomies. Most of these chapters give the results of postal questionnaires to surgeons involved. The third section, titled 'Advanced Techniques', starts with a chapter on how to perform the basic technique using the French method, which is out of place in a book of this nature There are further chapters on acute cholecystitis, acute biliary pancreatitis, cholangiography and sonography. The final section, on the complications of laparoscopic cholecystectomy and their management, contains two good chapters on laparoscopic bile duct injuries. Overall, as with most multiauthor texts, there is tremendous variation in the quality between the chapters. This book will be a useful addition to one's library but it is by no means essential.

C. M. S. Royston

Hull Royal Infirmary
Anlaby Road
Hull HU3 2JZ
UK

Notices and announcements

2–5 March 1997
11th Biennial Congress – Asian Surgical Association Congress
Hong Kong
Information: Congress Secretariat, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

3–21 March 1997
Hammersmith FRCS Course Part B (Surgery in General)
London, UK
Information. Wolfson Conference Centre, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

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